Particle deposition in replica healthy and emphysematous alveolar models using computational fluid dynamics

Edward Harding Jr

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PARTICLE DEPOSITION IN REPLICA HEALTHY AND EMPHYSEMATOUS ALVEOLAR MODELS USING COMPUTATIONAL FLUID DYNAMICS

By

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A Thesis Submitted
In Partial Fulfillment
Of the Requirement for the

Master of Science

In

Mechanical Engineering

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Acknowledgements

There are a number of people that I would like to extend special gratitude towards for helping me throughout my years at RIT. Some may have helped more than others, but all have been crucial to the process and I could never have done it without them.

First of all, I would like to thank my parents, Ted and Nancy, sister, Kimberly, and brother, Luke. Although you never had a real idea of what I have done the past two years, you have all been there to support and guide me along the journey.

I would like to thank my thesis adviser, Dr. Risa Robinson, for all of her help and support over the years. I could not have produced the quality of work without her knowledge and expertise of the subject matter, as well as her ability to write and craft words into a masterpiece. There are so many things that I will always remember, stories of your children, daily office visits, Friday lunches, Templeton, and Orlando to name a few. This has truly been an unforgettable experience and I can’t believe it is over.

The faculty at RIT has also played an important role and deserves special thanks, particularly Diane Selleck and the office staff. You have all been extremely helpful in answering every imaginable question and solving every problem I would throw at you, and always had a smile or joke along the way. Last, I owe Bill Finch many thanks for his computer expertise in solving my many server, software, and licensing issues.

Additional thanks are given to Evan Whitby of Chimera Technologies who provided me the absolute best technical support for the Fine Particle Model (FPM). Without his extreme generosity, this work could not have been completed.

Thank you all.

This work was completed with the support of the American Cancer Society (RSG-05-021-01-CNE).
Abstract

Particle deposition in the pulmonary region of the lung has gained increasing interest in the past years. Of particular interest are nano-sized particles, because they have the potential of crossing the blood-gas barrier and into the capillaries. Many factors contribute to how and where particles deposit, such as lung morphology, breathing conditions, fluid flow characteristics, and alveolar wall movement. These many factors make simulating particle deposition in the alveoli difficult. The experimental in vivo studies have commonly used micron sized particles and there is a lack of data for smaller sized particles. Due to these many factors, deposition in the pulmonary region is not well understood. Furthermore, little attention has been paid to the emphysematous lungs, which have characteristics quite different than the healthy lung.

In this work, healthy and emphysematous replica acinus models were created from human lung casts using a 3D reconstruction software package. The models were used for simulating the particle deposition due to diffusion using Fine Particle Model (FPM). The FPM program was validated against an analytical solution using a straight tube, before moving on to predict the deposition in the alveolar models. Two particle sizes, 1 and 3 nm, were used to understand and compare pure diffusion in the lung using concentration contours. Results showed the particle deposition rate (particles/s) to be higher in the emphysegic. However, deposition rate per area (particles/m^2s) was found to be higher in the healthy model. The deposition efficiency (% of particles that deposit) of the healthy model was greater than the emphysemic model, consistent with literature. Results were found to be lower than experimental in vivo measurements and whole lung model of local alveolar deposition (particles deposited in alveoli/particles entering alveoli) in comparison to our results in the pulmonary region, showing the importance of including axial diffusion effects. More work must be done experimentally and numerically before an understanding of deposition of particles of this size can be determined.
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1.1 Background

1.1.1 Basic Anatomy

The human lungs begin at the trachea and bifurcate into the left and right lungs. The human lung is comprised of five lobes, the left lung is divided into two lobes and the right lung is divided into three lobes. Each lobe is comprised of three sections: at the beginning of each branch is a bronchi, which transitions to become a bronchiole, and each bronchiole is terminated with an acinus (Figure 1.1(A)).

An acinus typically begins around the 17th generation and is defined as the region that starts when the first alveolus occurs and ends at the lung’s termination (Figure 1.1(B)). Alveoli are
surrounded by capillaries and are the location at which all gas exchange takes place between the blood and oxygen rich air.

1.1.2 Emphysema

According to the National Health Interview Survey, the prevalence of emphysema is 18 out of every 1000 persons in the United States (Adams et al. 2008), however, the Burden of Obstructive Lung Disease states the prevalence worldwide is nearly 10.1% (Buist et al. 2007).

In general terms, emphysema is the loss of elasticity of the lung due to destruction of the lung walls, which causes a permanent enlargement in the acinus region (Figure 1.2). Emphysema causes difficulty in breathing since the overall surface area for gas exchange is minimized. It is typically caused by smoking, which causes varying degrees when toxic particles are inhaled continuously. Currently there is no cure for emphysema, making the destructive nature of the disease irreversible.

1.2 Particles

1.2.1 Good vs. Bad Particles

Experimental data has shown particles are capable of depositing in the alveolar region and crossing the blood-gas barrier (Nemmar et al. 2002). Once particles cross this barrier, they have the potential to deposit anywhere by means of the network of blood vessels throughout the body. If these particles are toxic, cigarette smoke particles for example, they could cause adverse effects in the lungs and other regions of the body.

If the particles are therapeutic, a better understanding of the deposition can be helpful in eliminating invasive medicine, for example injections. A better understanding of deposition can
also lead to a more accurate understanding of the dose, and how much is necessary for treatment by inhalers.

1.2.2 Mechanisms of Particle Deposition

The understanding of where particle deposition occurs on the walls of the lungs and how much can help provide an explanation into the causes of diseases such as emphysema. There are three main mechanisms in which particles can deposit: diffusion, sedimentation, and impaction. Typically, larger particles are deposited due to impaction and sedimentation, where as smaller particles deposit due to diffusion.

Diffusion occurs when a particle travels from a high concentration to a lower concentration due to a concentration gradient (Figure 1.3). Deposition due to diffusion is based upon particle size, the smaller the particle then the higher the diffusion coefficient is for the particle. The diffusion coefficient can be used as a comparison to describe the ease in which a particle can diffuse; a smaller particle can diffuse a farther distance than a larger particle in the same amount of time. The lung geometry and breathing conditions also play a role in whether or not a particle will deposit by diffusion. For example, if a person holds their breath between inhalation and exhalation, the particle’s residence time, or the time allowed for the particle to reach the wall, is increased, increasing deposition by diffusion. On the other hand, if the volume of the alveolar sac is enlarged, as in the case of emphysema, the distance the particle must travel to reach the wall is increased, decreasing the deposition by diffusion. All parameters must be considered as a whole to determine the effect of disease on particle deposition by diffusion.

![Diffusion](image)

Figure 1.3: Example of how a particle deposits due to diffusion. (Snyder 2005)
Sedimentation is the gravitational forces inflicted upon the particle causing it to deviate from the path of the fluid and deposit (Figure 1.4). As for the case of deposition by diffusion, residence time and alveolar geometry play an important role in determining the amount of deposition by sedimentation. However, unlike diffusion, orientation of the alveolar sac will play a role in sedimentation, since the particle’s nature will be to move in the direction of gravity by sedimentation, whereas with diffusion the particle will move radially out from the source of the concentration, regardless of orientation.

![Sedimentation](image)

*Figure 1.4: Example of how a particle deposits due to sedimentation. (Snyder 2005)*

Last, deposition due to impaction happens when a particle’s inertia is too high to follow the fluid’s path around sharp contours (Figure 1.5). The momentum causes the particle to maintain the path in which it was traveling, rather than turn the corner with the flow. The particle’s momentum creates a collision into the wall and the particle deposits. Impaction plays a negligible role on deposition in the alveolar sac, in comparison to diffusion and sedimentation, because the particle’s velocity, and thus its inertia, is extremely small.
It is clear that geometry plays an important role in particle deposition; therefore it is critical that realistic lung morphologies are used when determining particle deposition. This is particularly important when investigating diseased lungs, since the geometry is significantly altered. Understanding all of these mechanisms combined, and their effects on particle deposition as the lung is changed with disease, is a key factor in improving inhaled drug delivery, which could help treat and cure diseases like emphysema, and eliminate invasive drug delivery procedures.
2 Chapter 2 Literature Review

Many researchers have taken interest in trying to understand the mystery which takes place during inhalation and exhalation inside of the lungs. It has been shown routinely that convection alone cannot be the cause for transport to the most distal walls of the lung, where gas exchange occurs. It is generally agreed upon that convection is responsible for airflow in the conducting airways, but convective motion decreases and gives way to diffusive motion as the airways multiply and flow rate diminishes (Paiva 1972, Scherer et al. 1972). In the alveoli, diffusion dominates, and at the alveolar walls, diffusion is the main mechanism for exchange of oxygen and carbon dioxide. Unlike for gas, the extent to which aerosol particles travel by diffusion down the airways or in the pulmonary region is not well understood. In our previous work, we showed that in the alveolar region, diffusive motion likely dominates for smaller particles (Harding and Robinson 2010, Berg et al. 2010). However, those studies focused on fluid flow and did not directly calculate particle deposition. To our knowledge, models of diffusive particle deposition in replica alveolar airways have not been presented in the literature.

For the purposes of our research, we review journal articles that used engineering models to analyze fluid flow in the distal regions of the lung, or acinar region. Particular attention was given to models which contained self terminating airways, in which details on alveolar shape and dimension were given. In addition, we review articles characterizing deposition due to diffusion and sedimentation in generalized geometries with simplified analytical formulas, and whole lung models that utilize these simplified deposition equations. Pulmonary deposition measurements in vivo are summarized for healthy subjects. Finally, the limited studies that have been done for particle deposition in emphysema, in vivo measurements and lung modeling, are reviewed.

Table 2.1 is comprised of some of the literature and the details which will be reviewed throughout this chapter.
Table 2.1: Summary of whole lung and alveolar models reviewed, including the model characteristics and deposition mechanism addressed in each study (N/A = Not applicable, D/MD = alveolar depth to mouth diameter ratio, X = covered in the study)

<table>
<thead>
<tr>
<th>Article</th>
<th>Alveolar Shape</th>
<th>Alveolar Radius (µm)</th>
<th>Duct Diameter (µm)</th>
<th>Expanding</th>
<th>Axisymmetric</th>
<th>Emphysema</th>
<th>D/MD</th>
<th>Diffusion</th>
<th>Sedimentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole Lung Models</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCRP (NCRP 1997)</td>
<td>Straight Tube Based on Haefelibleuer and Weibel (1988)</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trumpet (Yu, C. P. and Diu, C. K. 1983)</td>
<td>Straight Tube Based on Weibel (1964)</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPPD (Anjilvel and Asgharian 1995)</td>
<td>Straight Tube Based on Haefelibleuer and Weibel (1988)</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Alveolar Models</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tsuda et al. (1995)</td>
<td>Round - torus on tube</td>
<td>200</td>
<td>250</td>
<td>X</td>
<td>X</td>
<td>0.50 - 0.87</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darquenne (2001)</td>
<td>Round - Two dimensional Based on Haefelibleuer and Weibel (1988)</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haber et al. (2003)</td>
<td>Round - Hemisphere</td>
<td>X</td>
<td>X</td>
<td>0.5</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sznitman et al. (2007a)</td>
<td>Round - single bulb on tube</td>
<td>217</td>
<td>230</td>
<td>X</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumar et al. (2009)</td>
<td>Truncated octahedron</td>
<td>N/A</td>
<td>280</td>
<td>X</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Experimental</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Karl et al. (2004)</td>
<td>Square channel</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>0.17 - 1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oakes et al. (2010)</td>
<td>Round</td>
<td>122 - 140</td>
<td>N/A</td>
<td>X</td>
<td>0.4 - 0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berg et al. (2010)</td>
<td>Replica in vivo</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>0.98 – 1.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.1 Progression of Lung Models for Alveolar Flow

In the past, a number of various models have been used in numerical and experimental studies, however, due to a lack of knowledge it is difficult to understand or create an argument in which one model is superior to the next. Some of the first studies made use of axisymmetry to create simplistic models for comparison, whereas of lately the models have begun to move closer to what many may consider actual geometries. To this point, no one has obtained results numerically for actual in vivo geometries, which is one of the aims in this work.

In 1994, Tsuda et al. were one of the first groups to perform a numerical Computational Fluid Dynamics (CFD) study for a model representing the alveolar region with moving walls. In the following year, 1995, Tsuda et al. used a similar model best described as a straight tube combined with a larger torus representing an axisymmetric alveolus. The model wall expands and contracts rhythmically and is shown in Figure 2.1. The labels QA and QD are the alveolar and ductal flow rates, respectively. The radii of the duct and alveolus are depicted as RD and RA. Last, γ is explained to be the opening half angle. Two cases were tested, where one varied the ratio of the alveolar to ductal flow rates (QA/QD) while keeping the alveolar shape constant. The other case analyzed the importance of variance in the opening half angle. The study was shown to use a ductal radius of 250 µm and an alveolar radius of 200 µm, which can be used to calculate alveolar depth to alveoli mouth diameter (D/MD) ratios of 0.5 to 0.866.
Later, a CFD simulation study using FIDAP was completed to better understand particle transport and deposition in a multi-generation two-dimensional alveolated model (Darquenne 2001). Alveolar dimensions were based upon values published by Haefeli-Bleuer and Weibel (1988). Due to a lack in computational power, a central unit (shown in Figure 2.2) was solved in order to achieve inlet boundary conditions for each of the eight peripheral units, which were similar in feature. Drag and gravitational forces were applied to 2 µm diameter particles using a post-processor. Particle deposition was found to accumulate at the bifurcations of the model, which showed good agreement to experimental studies performed on lab rats (Brody and Roe 1983).

A rhythmically expanding self similar alveolus (Figure 2.3) was solved analytically for fluid and particle flow, along with particle deposition (Haber et al. 2003). In this study, diffusion was neglected and only effects of sedimentation were included. Particle sizes that were studied ranged from 0.5 to 2.5 µm in diameter while exploring the effects of the model’s orientation on sites of deposition.

In 2004, Karl et al. collaborated to publish their findings in an experimental study using Particle Image Velocimetry (PIV). The model used was an axisymmetric straight tube representing a duct with a series of outer channels to characterize the alveoli (Figure 2.4). Six different models were studied containing various dimensions for the channel width and orifice diameter while the duct diameter was kept constant. Based upon the given dimensions, D/MD ratios ranged from 0.17 to 1.0, where the alveolar mouth diameter was assumed to be represented by the channel width and the alveolar depth was considered to be half the difference between the duct and orifice diameters.
Sznitman et al. (2007a) was the first to show numerical results in a three dimensional non-axisymmetric model containing a single expanding alveolus (Figure 2.5). The duct diameter, $D_d$, length of the duct, $l_d$, and alveolus radius, $r_A$, were modified to generate models for the 8 distal generations of the lungs where dimensions were based upon Weibel (1965). The dimensions of Sznitman’s eighth generation, or Weibel’s 23rd, were 230 µm for a duct diameter and 217 µm for an alveolus radius. Using the given dimensions resulted in a $D/MD$ ratio of 0.9. Results stated the critical $Q_A/Q_D$ ratio of 5.6%, to govern the difference between recirculatory and radial flow.

2.2 Three Dimensional (3-D) Terminating Models for Alveolar Flow

Kumar et al. (2009) published their work of numerical simulations on models created by the construction of multiple truncated octahedrons (3 hexahedral faces and 5 square faces) for alveoli. Three cases were analyzed to depict various regions of the lower lung, however only two of the cases were of interest. The first case of interest looked at the 2-3 generations proximal to 23rd generation (Figure 2.6(A)). Of most interest, the last case contained a self terminating alveolar sac (Figure 2.6(B)), which is the very similar to the models used by Oakes et al. (2010) and my published work (Harding and Robinson 2010). Unfortunately, due to the complexity of the building blocks of this model, dimensions of an individual alveolus are unknown. Kumar et al. (2009) does publish the overall length to be 1045 µm and an alveolar duct diameter of 280 µm.
Using a similar alveolar building block as Kumar et al. (2009), Sznitman et al. (2009) used truncated octahedrons (8 hexagonal and 6 square faces), or 14-hedra, to build a 3D space filling tree. A CFD analysis was performed on the expanding model to simulate fluid and particle flow. The results showed recirculation to be present in generations labeled 3-5, and reversible flow in terminal generations (6-8) where the flow rate ratio was greater than 0.02. Particle flow was analyzed for particle diameters of 1 and 3 µm, where results showed the 3 µm to be largely affected by gravitational settling and the 1 µm particles to have longer residence times and be driven primarily by convection. Additionally, the authors looked at the effects of model orientation on particle deposition using 1 and 3 µm particles in the model shown in Figure 2.5, which had dimensions that correlated to the 5th generation (Weibel’s 20th). The results for this model were very similar to that of the acinar tree.

Recently work has been published on flow fields in a compliant acinus replica model using PIV techniques (Berg et al. 2010). The model used in this study was based upon a lung cast obtained from a human cadaver and had been reconstructed using medical illustration techniques (Figure 2.8). This was the first study which analyzed in vivo replica geometry. Results of this study found reversible fluid flow fields throughout the model under all conditions analyzed. A Péclet
number analysis showed the movement of 0.01 and 0.1 µm particles to be dominated by diffusion in all locations other than the inlet.

![Figure 2.8: 3D human acinus replica model obtained from medical illustrations of a human lung cast. (Berg et al. 2010)](image1)

![Figure 2.9: 3D expanding self terminating alveolar sac created using Weibel (1964) geometry. (Harding and Robinson 2010)](image2)

Last, my work has been published which examined the fluid flow in an expanding self terminating 3D alveolar sac using CFD (Harding and Robinson 2010). Different from Kumar et al. (2009) and Sznitman et al. (2007b, 2009), the model uses spherical caps to represent alveoli (Figure 2.9). The dimensions for creating the model were based upon Weibel (1964) geometry, possessing a duct diameter of 0.23 mm and alveoli radii of 0.091 mm along the duct with D/MD ratios of 1.09. Results for the fluid flow were found similar to Berg et al. (2010), reversible flow in all regions of the model. A Péclet number analysis showed that 0.01 and 0.1 µm particle motion would be dominated by diffusion in all regions other than the model’s inlet.

2.3 Simple Diffusion and Whole Lung Models

Whole lung dosimetry models utilize many simplifying assumptions, including straight tubes, average velocities, uniform expansions, no axial diffusion, and mixing of tidal and residual air: International Council of Radiation Protection - ICRP (Bates et al. 1966), National Council of Radiation Protection - NCRP (NCRP 1997), Trumpet (Yu and Diu 1983), and Multiple Particle Path Dosimetry - MPPD (Anjilvel and Asgharian 1995). Error gets introduced due to the straight tube assumptions in the alveolar region. The entire alveolar region is modeled as a single open straight tube. Figure 2.10 shows the total (Tot.), tracheobronchial (TB), and pulmonary (Pulm.)
deposition fractions versus particle size for a breathing frequency of 15 breaths per minute and a tidal volume of 500 ml. Other input parameters necessary for generating this data are included in Table 2.2.

Figure 2.10: Total (Tot.), tracheobronchial (TB), and pulmonary (Pulm.) deposition fractions vs. particle size for MPPD and Trumpet whole lung models.

Table 2.2: Input Parameters for Deposition Models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRC (mL)</td>
<td>3200</td>
</tr>
<tr>
<td>TV (mL)</td>
<td>500</td>
</tr>
<tr>
<td>Breathing Frequency (breaths/min)</td>
<td>15</td>
</tr>
<tr>
<td>Period (sec)</td>
<td>4</td>
</tr>
<tr>
<td>% Inhale (sec)</td>
<td>39% (1.56)</td>
</tr>
<tr>
<td>% Pause (sec)</td>
<td>4.9% (0.20)</td>
</tr>
<tr>
<td>% Exhale (sec)</td>
<td>56.1% (2.24)</td>
</tr>
</tbody>
</table>
For decades, straight tubes have been commonly used to represent airways and model the flow in these airways. Previous work has provided analytical formulas for calculating deposition efficiencies due to diffusion for flow in tubes. Ingham (1975, 1984, 1991) has developed diffusion efficiency equations for inlet flow conditions such as uniform, slug, and parabolic profiles, assuming no axial diffusion. The equations generated from Ingham are used in the whole lung models, MPPD and Trumpet, previously discussed. Because axial diffusion was not included in these deposition efficiency formulas, tracheobronchial deposition of nanosized particles will be overestimated and the transport of these particles to the alveolar region will be underestimated. In 1994, Chen published work that derived an analytical solution for diffusion in a self terminating, or single closed end tube, with axial diffusion. These formulations have not been incorporated into the whole lung deposition models.

Robinson, Snyder, and Oldham (2007) used the analytical formulas from Ingham (1975, 1991) to validate solutions of diffusion using flow in a straight tube generated by Fine Particle Model (FPM). Unfortunately no work has been done to validate FPM’s solutions for diffusion in a self terminating model, similar to the alveolar region of the lung.

### 2.4 Measurements of Pulmonary Deposition for Healthy Humans In vivo

There have been a select number of studies that have looked at and reported particle deposition efficiency in the alveolar region of the lungs. Table 2.3 summarizes some of the studies, which are described in more detail below.

Chan and Lippmann (1980) collected deposition data from 26 healthy, non-smoking subjects. Tests were performed, which had the subjects inhale a tidal volume of 1000 ml at a breathing frequency of 14 breaths per minute, using 0.2 – 0.7 µm particles. Breathing was controlled through audible signals, with pauses discouraged. Exact data was not reported for deposition with respect to particle size, so creating a plot was not achievable. However, the results from Figure 7 in their report show the results for pulmonary deposition are in good agreement with the ICRP model (ICRP 1994). The quality of this figure was not good, so it was not included.

Paiva et al. (1977) used a group of 48 smoker and 2 non-smoker males to analyze deposition of 5 +/- 0.7 µm particles. Subjects were randomly assigned tidal volumes ranging between 0.11 and 0.8 liters which was controlled and monitored. Only a single breath was studied, which required
a pause of 3 seconds between inhale and exhale. Alveolar deposition was estimated based upon nomogram predictions, with no exact results reported.

Emmett et al. (1982) performed experiments on a group of 12, consisting of 10 non-smokers, 1 pipe smoker and 1 light smoker. Monodisperse polystyrene particles ranging in size from 3.5 to 10 µm, which had densities between 1030 and 1060 kg/m³, were created by air driven spinning and coating with Tc. The subjects took 10 breaths per minute with a tidal volume of 1 L. The alveolar deposition results are shown in Figure 2.11.

In an older experiment, the deposition in 34 subjects, 33 males and 1 female, was analyzed (Lippmann and Albert 1969). Monodisperse, 1.3 to 7.9 µm diameter, insoluble iron oxide spheres tagged with Au or Tc were produced with spinning disc generators. The subjects were prompted by an audible signal to take 14 breaths per minute, whose alveolar deposition results are shown in Figure 2.12.
Table 2.3: Summary of experimental studies reporting pulmonary deposition vs. particle size. (N/A = Not applicable, NR = Not reported)

<table>
<thead>
<tr>
<th>Study</th>
<th>Breathing Frequency</th>
<th>Subjects</th>
<th>Number of Subjects</th>
<th>Particles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan and Lippmann (1980)</td>
<td>14 breaths/minute</td>
<td>healthy, non-smokers</td>
<td>NR</td>
<td>26</td>
</tr>
<tr>
<td>Emmett et al. (1982)</td>
<td>10 breaths/minute</td>
<td>10 non-smokers, 1 light smoker, 1 pipe smoker</td>
<td>M</td>
<td>12</td>
</tr>
<tr>
<td>Lippmann and Albert (1969)</td>
<td>14 breaths/minute</td>
<td>11 non-smokers, 4 ex-smokers, 18 smokers</td>
<td>33 M, 1 F</td>
<td>34</td>
</tr>
<tr>
<td>Pavia et al. (1977)</td>
<td>N/A</td>
<td>48 smokers, 2 non-smokers</td>
<td>M</td>
<td>50</td>
</tr>
<tr>
<td>Stahlhofen et al. (1980)</td>
<td>NR</td>
<td>non-smokers</td>
<td>M</td>
<td>3</td>
</tr>
<tr>
<td>Stahlhofen et al. (1981)</td>
<td>7.5 breaths/minute</td>
<td>healthy</td>
<td>7 M, 2 F</td>
<td>9</td>
</tr>
<tr>
<td>Kim and Jaques (2000)</td>
<td>15 breaths/minute</td>
<td>healthy</td>
<td>half M, half F</td>
<td>22</td>
</tr>
</tbody>
</table>
Figure 2.11: Alveolar deposition measured in a group of twelve people, breathing at 10 breaths per minute.

Figure 2.12: Plot showing the distribution of alveolar deposition for different particle sizes in 34 persons, breathing at 14 breaths per minute.
Stahlhofen et al. (1980) studied 3 healthy non-smoking males using a controlled method of delivery. One of the male subjects was tested using two different flow rates, which produced 4 collection trials. Alveolar particle deposition was measured for particle sizes ranging from 1 to 10 µm, with flow rates ranging anywhere from 250 to 750 ml/s, while the periods were either 2 or 4 seconds. All trials followed a similar trend with a maximum deposition peak at a particle diameter 3 µm, and sloping down on either side (Figure 2.13).

Most recently, Kim and Jaques (2000) used di-2-ethylhexyl sebacate vapor on non-hygrosopic metallic nuclei particles to test a focus group of 22, half male and half female, ranging in age from 20 to 40 years of age. Four particle sizes, 0.04, 0.06, 0.08 and 0.1 µm were used to analyze alveolar particle deposition. A controlled experiment was conducted which had the subjects inhale a tidal volume of 500 ml every 4 seconds, or 15 breaths per minute. The average results for the 11 men and 11 women are shown in Figure 2.14.

![Figure 2.13: Plot showing the trends of alveolar deposition vs. particle deposition in three subjects, for breathing period of 2 and 4 seconds.](image-url)
Figure 2.14: Average alveolar deposition results in 11 men and 11 women for four particle sizes, at 15 breaths per minute.

Figure 2.15: Combined experimental results on logarithmic axis for alveolar deposition versus particle size with lines of best fit showing trends.
As can be seen in Figure 2.15 and Figure 2.16 above, alveolar deposition for similar particles is not repeatable or understood. Additionally, more experimental research using smaller particles could be helpful in understanding the overall trends, especially nanosized particles (< 1 µm). Figure 2.17 compares the experimental results to pulmonary deposition predictions using the whole lung models. It is quite apparent there is a lack of agreement in micron sized particles; however the few data points near 0.1 µm and lower have similar trends to the whole lung models. It is quite possible that the very low deposition efficiency predicted for the alveolar region is not accurate. As discussed in Section 2.3, neglecting axial diffusion could introduce errors in these predictions for nanosized particles. *In vivo* data is required to verify these whole lung model predictions.
2.5 Evidence of Decreased Deposition in Emphysema

2.5.1 Emphysemic Lung Models

Sturm and Hofmann (2004) examined particle deposition by the combination of sedimentation and diffusion using an improved Monte Carlo computer code (Koblinger and Hofmann 1990) in various models of different degrees of emphysema. This was a whole lung model, in which the tracheobronchial region was adjusted to represent COPD (chronic obstructive pulmonary disease) and the alveoli were adjusted to simulate various types of emphysema (Figure 2.18). This model is 2D in the alveolar region and one dimensional (axial) in the TB region. Axial diffusion was not considered directly in this model,

Figure 2.17: Plot comparing whole model pulmonary deposition predictions to actual experimental pulmonary deposition. (Refer to legend in Figure 2.15 for experimental data)

Figure 2.18: Various models used to investigate effect of alveolar shape based upon emphysema. (A) Normal, (B) Centriacinar, (C) Paraseptal, and (D) Panacinar (Sturm and Hofmann 2004)
allowing for the possibility that transport of smaller particles to the alveolar region is likely underestimated, which in turn underestimates alveolar deposition. Air mixing in the alveolar region is modeled with constant mixing factor based on empirical data.

Particle sizes ranging from 0.001 to 10 µm in diameter were analyzed in generations ranging from the 12th to terminal. The published results showed that particles only were able to diffuse to the openings of the alveoli and not to the walls during a four second period. Particle deposition was shown to be higher in the healthy model compared to models representing various types of emphysema. Alveolar deposition was very low for small particles; however it is not clear from the article if this is due to filtering in the tracheobronchial (TB) region, since neither total nor TB deposition was reported. However, since plots of alveolar deposition for healthy are similar to other whole lung models, the small alveolar deposition predicted here could be due to proximal airway filtering.

Oakes et al. (2010) presented work on an experimental PIV study in the most distal region of the lung and compared the flow characteristics between a healthy and emphysemic alveolar sac. At the time, this was one of the first attempts to look at a non-axisymmetric expanding model experimentally. The number of alveoli varied from thirteen for the healthy model and seventeen for the emphysema model (Figure 2.19). The average D/MD ratios were computed to be 0.66 and 0.4 for the healthy and emphysematous models, respectively. The overall alveolar sac lengths were 0.748 mm, while the alveolar radii were given to be 122 µm and 140 µm, again respectively. Based upon the results, deposition due to diffusion was estimated to be greater in the healthy model in comparison to the emphysema model.
2.5.2 Experimental Deposition for Emphysema

Kohlhauff et al. (1997) performed an experimental study on 29 subjects who possessed pulmonary emphysema. A 25 ml bolus of 0.9 µm diameter particles was inserted as patients inhaled to lung depths of 200, 400, 600, and 800 ml. The patients then exhaled until the entire bolus was recovered or until residual volume was achieved. Results were compared to a similar study performed on 79 healthy patients (Brand et al. 1997), which showed the bolus dispersion to be greater in patients with emphysema. The researchers had a number of hypotheses as to the reasoning for these results: airway blockage, unequal spread of the disease, and uneven ventilation.

2.6 Gaps in the Literature

A replica in vivo model of the alveolar region has never been used in a CFD simulation to solve for particle transport by pure diffusion. Using replica geometry is helpful in understanding the effects of the particle transport mechanisms of diffusion which helps explain how tidal air is able to travel to alveolar walls for carbon dioxide-oxygen exchange with the capillaries. Most researchers have used idealized geometries to predict deposition calculations in these complex geometries; therefore, it is thought that this work gives a closer prediction to the actual deposition. In the majority of previous studies, only a single deposition mechanism was analyzed. Haber et al. (2003) states that even though their study neglects the stochastic Brownian force exerted on a moving particle, the influence relative to the gravity force, especially on small particles 0.5 µm in diameter, is still in dispute (Heyder et al. 1985) and might prove to be potentially important.

Some insight into alveolar particle deposition has been provided by experimental research in healthy subjects, however, rarely studies have looked at deposition of nanosized particles (less than 1 µm), as was done in this work, and never due to diffusion only. In addition, only a few studies have looked at how the differences in healthy and emphysematous alveolar sac geometry affect particle transport. This research helps to further shed light on these unknowns.

This research was designed to help in understanding the phenomena of how nanoparticles are able to reach alveolar walls in the distal regions of the lung. Unfortunately, experimental results are difficult to obtain due to the extremely small size of alveoli and the complex geometries that
would be required for accurate deposition. Because of this, computers are necessary for moving research forward. The comparison provided between replica healthy and diseased models will further contribute to how the changes in geometry affect deposition.

2.7 Scope of Research

The goal of this research was to gain a better understanding of diffusive particle transport in the alveolar region and to evaluate the effect of diseased lung geometry on particle deposition by diffusion. The following aims were necessary for completion of this work:

Specific Aim 1

To create healthy and emphysematous human models to be used in a Computational Fluid Dynamics (CFD) study by means of lung casting, Scanning Electron Micrograph (SEM), Computed Axial Tomography (CT) scanning, reconstruction, geometry cleanup, and meshing.

Specific Aim 2

To validate and perform a CFD analysis on healthy and emphysematous models to determine the particle concentration as a function of time and position and the particle deposition due to diffusion.

Specific Aim 3

Compare healthy and emphysematous simulation results to each other, experimental in vivo deposition results in literature, and whole lung model solutions from literature.
3 Chapter 3 Theory and Validation

3.1 Brownian Diffusion and Convective-Diffusion Equation

Brownian motion is the random motion of an aerosol particle in still air caused by random variations in the relentless bombardment of gas molecules against the particle (Hinds 1999). Diffusion is the mass transfer of particles from a higher concentration region to a lower. Fick’s first law of diffusion states that the mass transfer by molecular diffusion is proportional to the diffusion coefficient. If the diffusion coefficient is uniform in all directions, Fick’s law can be defined as

\[ J = -D \nabla C \] (3.1)

where \( J \) is the flux (particles/m² s), \( D \) is the diffusion coefficient (m²/s), and \( C \) is the particle concentration (particles/m³). If Fick’s first law is applied to a finite volume element, along with the conservation of mass theorem, the convective-diffusion equation can be derived (Gebhart 1993),

\[ \frac{\partial C}{\partial t} = D \nabla^2 C + C''' \] (3.2)

where \( t \) is time and \( C''' \) is the internal mass generation and storage in the control volume. If applied to a cylindrical domain, the equation becomes

\[ \frac{\partial C}{\partial t} = D \left[ \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial \phi^2} + \frac{\partial^2 C}{\partial z^2} \right] + C''' \] (3.3)

If no mass generation is present and the model’s boundaries are axisymmetric, then Equation (3.3) can be reduced to

\[ \frac{\partial C}{\partial t} = D \left[ \frac{\partial^2 C}{\partial r^2} + \frac{1}{r} \frac{\partial C}{\partial r} + \frac{\partial^2 C}{\partial z^2} \right] \] (3.4)

Equation (3.4) can be solved for particle concentration in a cylinder, \( C(r, z, t) \). With knowledge of this, Equation (3.1) can be used to find the total rate of particle diffusion to the wall (particles/s) by integrating over the area,

\[ J'_{wall} = - \int_0^L D \frac{\partial C}{\partial r} \bigg|_{wall} 2\pi R dz \] (3.5)
where $L$ is the cylinder length, and the inlet of the model can be represented as

$$J'_{inlet} = \int_0^R D \frac{\partial C}{\partial z}|_{inlet} 2\pi rdr$$

(3.6)

where $R$ is the cylinder radius. The concentration gradients found in Equations (3.5) and (3.6) can be evaluated using a second order accurate discretization that can be found in Tannehill (1997),

$$\frac{\partial C}{\partial \hat{x}} = \frac{3C_i - 4C_{i+1} + C_{i+2}}{2\Delta \hat{x}}$$

(3.7)

where $C_i$ is the concentration at the node of interest, and $\hat{x}$ is the direction normal to the direction of diffusion.

Using Equations (3.5) and (3.6), the rate at which particles deposit on the wall (particles/s) and enter the cylinder (particles/s) can be calculated, which when summed over time, $T$, can be used to calculate the total number of particles depositing on the wall,

$$\text{Particles deposited} = \int_0^T J'_\text{wall} \, dt = -D \int_0^T \int_0^L \frac{\partial C}{\partial r}|_{\text{wall}} 2\pi Rdz \, dt,$$

(3.8)

and entering the cylinder,

$$\text{Particles entered} = \int_0^T J'_{inlet} \, dt = -D \int_0^T \int_0^R \frac{\partial C}{\partial z}|_{inlet} 2\pi rdr \, dt.$$  

(3.9)

The deposition efficiency in the straight cylinder can then be found from

$$\text{Deposition Efficiency} = \beta = \frac{\text{Particles deposited}}{\text{Particles entered}} \times 100\%.$$  

(3.10)

### 3.2 Analytical Solution for a Closed-End Cylinder

A normalized analytical solution has been derived for the concentration as a function of position and time in a straight cylinder geometry possessing a constant inlet concentration and the walls having zero concentration in Chen (1994).
The entire derivation can be found in the thesis of Chen, which shows the normalized solution as

\[
\sigma(r, \theta, z) = \sigma_1(r, \theta) + \nu(r, \theta, z) = \sum_{m=1}^{\infty} \frac{2 \sinh \left( \frac{D_m \alpha}{\alpha} \eta \right)}{D_m J_1(D_m) \sinh \left( \frac{D_m}{\alpha} \right)} + \sum_{m=1}^{\infty} \sum_{n=0}^{\infty} \frac{4 \alpha^2 \pi \cos(n \pi) J_0(D_m \eta) \sin(n \pi \eta)}{D_m J_1(D_m) \left( D_m^2 + \alpha^2 \pi^2 \right)} \exp \left[ -(D_m^2 + \alpha^2 \pi^2) \tau \right]
\]

(3.11)

where the normalized relations are

\[
\sigma = \frac{C}{C_0}; \quad \gamma = \frac{r}{r_0}; \quad \eta = \frac{z}{l_0}; \quad \tau = \frac{D}{r_0^2} t; \quad \alpha^2 = \frac{r_0^2}{l_0^2}
\]

and \(D_m\) are the eigenvalues which satisfy the equation

\[
J_0(D_m) = 0, \quad (m = 1, ..., \infty)
\]

(3.12)

The solution to this equation was used to validate the Fine Particle Model (FPM). First, the solution was tested to determine the effect of summation number and grid spacing, as described in the following sections. The normalized concentration was found from Equation (3.11) and the normalized concentration gradients were found from
\[
\frac{\partial \sigma}{\partial \gamma} = \frac{3\sigma_{i,j} - 4\sigma_{i,j+1} + \sigma_{i,j+2}}{2\Delta \gamma}
\]  

(3.13)
at the wall, and

\[
\frac{\partial \sigma}{\partial \eta} = \frac{3\sigma_{i,j} - 4\sigma_{i+1,j} + \sigma_{i+2,j}}{2\Delta \eta}
\]  

(3.14)
at the inlet, as previously discussed. Rate of particle diffusion to the wall (particles/s) was found using

\[
J'_{\text{wall}} = -\sum_{i=0}^{Nz} D \left. \frac{\partial \sigma}{\partial \gamma} \right|_{i,j=\text{wall}} 2\pi d\gamma
\]  

(3.15)
where \(Nz\) is the number of nodes in the \(\eta\) (normalized \(z\)) direction of the mesh. Rate of particle diffusion through the inlet (particles/s) was found from

\[
J'_{\text{inlet}} = \sum_{j=0}^{Nr} \left. \frac{\partial \sigma}{\partial \eta} \right|_{i=\text{inlet},j} 2\pi \gamma_j d\eta
\]  

(3.16)
where \(Nr\) is the number of nodes in the \(\gamma\) (normalized \(r\)) direction of the mesh, and \(\gamma_j\) is the normalized radius value at which the calculation is taking place.

### 3.2.1 Analysis on the Effects of the Number of Summations on Concentration Gradient and Flux

In order to obtain an analytical solution, a series of summations takes place in the steady and unsteady terms. A study was performed to better understand if the number of summations has an effect on the final solution of \(\sigma\), and if so, what is the critical number of summations before the solution converges.

#### 3.2.1.1 Steady Summation Effects

The steady portion of the analytical equation was first analyzed by reviewing the concentration gradients at the model wall and inlet with increasing numbers of summations (Equation (3.11)). Figure 3.2 shows the concentration gradients near the wall over the length of the model for increasing summations. The concentration gradient values are shown to converge as \(\eta\) approaches 0.1.
Figure 3.2: Steady summation effects on the concentration gradient near the wall. (Numbers of summations shown in parenthesis.)

A closer look at the wall concentration gradients closest to the inlet (Figure 3.3) helps to show as the summation number increases and approaches 100, the concentration gradient values begin to converge.

Figure 3.3: A zoomed in look at the concentration gradients closest to the model inlet helps to show values are unaffected by summation number as $\eta$ increases. (Numbers of summations are shown in parenthesis.)
Figure 3.4 shows the same region as above, however, the summation numbers have been increased to better show the convergence of concentration gradient. The concentration gradient at the wall is converged after 150 summations.

![Steady Summation Effects near Wall](image)

**Figure 3.4:** A second zoomed in view of the concentration gradients near the model inlet, however, with higher summation numbers. A total of 150 steady summations are shown to be fully converged. (Numbers of summations are shown in parenthesis.)

The analysis of summation effects on the inlet concentration gradient showed some interesting results. The results demonstrated a sinusoidal trend at the model inlet during low total summation numbers (Figure 3.5), however, this trend was smoothed out as the number of summations was increased (Figure 3.6). The sinusoidal trend is caused by the Bessel functions found in Equation (3.11), which spans the radial direction. The Bessel functions do not have any effect on the wall concentration gradient since the $\gamma$ value is constant. Similar to the wall concentration gradient, the inlet concentration gradient was shown to converge after 150 summations.
Figure 3.5: Sinusoidal trend of inlet concentration gradient for low summation totals. The trend is shown to be less drastic as the number of summations increases. (Numbers of summations shown in parenthesis.)

Figure 3.6: Inlet concentration gradient has fully converged after 150 steady summations. (Numbers of summations are shown in parenthesis.)
3.2.1.2 Unsteady Summation Effects

A similar study was performed on the unsteady portion of the equation, using a total of 150 summations to solve for the steady state term. Although the unsteady term has two summations that take place, the number of summations for each remained the same for consistency. The results for wall and inlet flux for each number of summations were used as a method of determining convergence.

The summation effects on the wall flux were found to be very insignificant after a time of 0.7 seconds, with all values becoming equal regardless of summation number. Therefore the analysis was refined to only the first 0.7 seconds, which showed after 100 summations the results for wall flux remained constant with increasing summations (Figure 3.7).

![Unsteady Summation Effects on Wall Flux](image)

*Figure 3.7: The number of unsteady summations is shown to no longer have an effect on the wall flux after 0.7 seconds. Prior to 0.7 seconds, 100 or greater unsteady summations are needed to ensure a converged solution near the wall. (Numbers of summations are shown in parenthesis.)*

The inlet flux findings were slightly different than those found for the wall flux. After 1 second, the inlet flux became unaffected by the number summations that were used to calculate it. It was not until a total of 175 summations occurred before the inlet flux had converged for times prior to 1 second (Figure 3.8).
Based upon the results presented, a total of 150 steady summations and 175 unsteady summations were used in all further analyses and validations of the Fine Particle Model (FPM).

![Unsteady Summation Effects on Inlet Flux](image)

*Figure 3.8: The number of unsteady summations is irrelevant after 1 second, as is shown by all points being equal after this point in time. Unlike the wall flux, in order for a converged solution at the inlet to occur, at least 175 unsteady summations must take place. (Numbers of summations are shown in parenthesis.)*

### 3.2.2 Analysis on the Effects of Grid Spacing

An analysis was conducted to determine the effects of grid spacing on Chen’s analytical model. Since the model calculates the value at each point in the grid individually, the values of concentration are unaffected by spacing. However, it was shown that as grid spacing values get smaller than 0.005 (200 x 200 elements), the values of concentration gradient begin to become unstable near the model’s inlet (Figure 3.9). This in turn causes some instability in the calculation of the inlet concentration gradient.
Although instability is introduced as the number of nodes increases, some benefit does exist with the increase in nodes. As the number of nodes increases, the inlet and wall flux values converge (Equations (3.15) and (3.16)). This can be explained by the increase in the number of points used for calculation; outlying points have a smaller effect on the total. To eliminate the regions of instability near the inlet, the nodes located at $\eta=0.01$ and 0.02 were used for calculating the concentration gradient when calculated for grid spacing’s of 0.005 and below. Similarly, the nodes located at $\gamma=0.98$ and 0.99 were used to calculate the wall concentration gradient. Using the normalized concentrations at the nodes located near the wall and inlet to calculate the normalized concentration gradients, a normalized flux could be calculated for each using Equation (3.1) and summing over the respective area. Based upon Figure 3.10, it was decided that a grid spacing of 0.005 was satisfactory for use in further analysis.
3.3 Application of Fine Particle Model (FPM) to a Closed-end Tube

3.3.1 FPM Theory and Equations

The Fine Particle Model (FPM) is an add-on used by the CFD program, Fluent, to calculate the motion of particles. FPM solves an equation known as the Moment Dynamics Equation (MDE). The MDE is defined as

$$\frac{\partial M_{jk}}{\partial t} = \text{conv}_{jk} + \text{ext}_{jk} + \text{diff}_{jk} + \text{coag}_{jk} + \text{cond}_{jk} + \text{nuc}_{jk} + \text{src}_{jk}$$

(3.17)

in which $M_{jk}$ is the $k^{th}$ moment of mode $j$. Equation (3.17) accounts for the external processes of convective transport (conv), transport by external forces (ext), diffusion (diff), along with internal processes such as coagulation (coag), condensation and evaporation (cond), homogeneous nucleation (nuc), and general source terms (src) (Chimera 2005). In the proposed work, only diffusion and the external process of sedimentation will be analyzed, reducing Equation (3.17) to,
\[
\frac{\partial M_{j,k}}{\partial t} = \text{ext}_{j,k} + \text{diff}_{j,k}, \tag{3.18}
\]

The size distribution moment term, \(M_{j,k}\), is solved for using the “method of moments”, where integral moments of the modes are represented as additional scalars in FLUENT,

\[
M_{j,k} = \int_{0}^{\infty} m_{p}^{k} n_{j}(m_{p})dm_{p} \tag{3.19}
\]

where \(j\) is the mode number and \(k\) is the moment average of the particle distribution (where 1, 2, and 3 correspond to particle size, surface area, and mass, respectively), \(n_{j}\) is the lognormal size distribution of particles for mode \(j\), and \(m_{p}\) represents the single particle mass.

The external force term, \(\text{ext}_{j,k}\), can be used to include processes like thermophoresis, sedimentation, and electrical and magnetic forces, by substituting various forms of the size-dependent external velocity, \(u_{\text{ext}}\), into \(\text{ext}_{j,k}\) to yield

\[
\text{ext}_{j,k} = -\nabla \cdot \left[ \bar{u}_{\text{ext},j,k} M_{j,k} \right] \tag{3.20}
\]

where

\[
\bar{u}_{\text{ext},j,k} = M_{j,k}^{-1} \int_{0}^{\infty} m_{p}^{k} u_{\text{ext}}(m_{p}) n(m_{p})dm_{p} \tag{3.21}
\]

is the moment-averaged external velocity of the \(k\)th moment of mode \(j\) (Chimera 2005).

Sedimentation, also called gravitational settling, is caused by the effect of gravitational acceleration on particles, in which the particle size-dependent external velocity is expressed as,

\[
u_{\text{ext, sed}}(m_{p}) = \frac{\rho_{p,j} C_{s}(Kn) d_{p}^{2}}{18 \eta_{g}} g \tag{3.22}
\]

where \(\rho_{p,j}\) is the particle density of the mode \(j\), \(d_{p}\) is the particle diameter, \(\eta_{g}\) is the gas dynamic viscosity, and \(g\) is the vector of gravitational acceleration (Chimera 2005, Hinds 1999). \(Kn\) is the Knudsen number defined as,

\[
Kn = \frac{2 \lambda_{g}}{d_{p}} \tag{3.23}
\]

where \(\lambda_{g}\) is the mean free path of the gas molecules (Hinds 1999). Last, \(C_{s}(Kn)\), in Equation (3.22), is the Cunningham slip correction factor that corrects for the degree to which gas molecules “slip” over the particle’s surface. The slip correction is characterized as
Diffusion is the transport of particles by random motion caused by thermal collisions with gas molecules, the well-known “Brownian motion”. It is represented in the FPM as the $\text{diff}_{j,k}$ term in the MDE, or Fick’s Law, whereas in Fluent’s Discrete Phase Model (DPM) the effect of diffusion is represented as an additional, random particle velocity. The diffusion term in the FPM is represented as

$$\text{diff}_{j,k} = \nabla \cdot \left[ \rho_g \bar{D}_{j,k} \frac{M_{j,k}}{\rho_g} \right]$$

(3.25)

where $\rho_g$ is the gas density and the $k^{th}$ moment diffusivity of mode $j$, $\bar{D}_{j,k}$ is given by

$$\bar{D}_{j,k} = M_{j,k}^{-1} \int_0^\infty m_p^k D_p(m_p) n(m_p) dm_p$$

(3.26)

and the particle diffusion coefficient can be expressed as

$$D_p(m_p) = \frac{k_B T}{3 \pi \eta_g d_p} c_s(Kn)$$

(3.27)

where $k_B$ is the Boltzmann constant (Chimera 2005, Hinds 1999). This term varies by particle size only, and is constant for any one particle size, therefore will be denoted as $D$ for the remainder of the theory.

The size distribution moment term, $M_{j,k}$, in Equations (3.17-21, 3.25, and 3.26) can be simply reduced to being the particle concentration, $C$, when a monodisperse group of particles is used, in which only a single mode would exist ($j=1$) without any size distribution ($k=1$). Using this simplification, Equation (3.18) becomes the governing equation,

$$\frac{\partial C}{\partial t} = -\nabla \cdot [\bar{u} C] + \nabla \cdot \left[ \rho_g \bar{D} \frac{C}{\rho_g} \right]$$

(3.28)

and Equation (3.19) becomes

$$C = \int_0^\infty m_p n(m_p) dm_p$$

(3.29)

When Equations (3.21) and (3.26) are substituted into Equation (3.28), it becomes,
Using the right hand side of Equation (3.29) to simplify, Equation (3.30) reduces to

\[
\frac{\partial C}{\partial t} = -\nabla \cdot \left[ C^{-1} \int_0^\infty m_p u_{ext,sed} (m_p) n(m_p) dm_p \ C \right] \\
+ \nabla \cdot \left[ \rho_g C^{-1} \int_0^\infty m_p D n(m_p) dm_p \ \nabla C \ \rho_g \frac{C}{\rho_g} \right] 
\]  
(3.30)

Using the right hand side of Equation (3.29) to simplify, Equation (3.30) reduces to

\[
\frac{\partial C}{\partial t} = -\nabla \cdot \left[ C \ u_{ext,sed} \right] + \nabla \cdot \left[ \rho_g D \ \nabla C \ \frac{C}{\rho_g} \right] 
\]  
(3.31)

Combining the divergence terms, Equation (3.31) becomes,

\[
\frac{\partial C}{\partial t} = \nabla \cdot \left[ D \ \nabla C - C \ u_{ext,sed} \right] 
\]  
(3.32)

Last, if the carrier gas is incompressible and Newtonian, \( \rho_g \) and \( \eta_g \) will not change with position and a final reduction yields

\[
\frac{\partial C}{\partial t} = \ \text{molecular diffusion} - \text{gravitational settling} 
\]  
(3.33)

which can be used to solve for the concentration in the flow field as a function of time, due to molecular diffusion and gravitational settling. FPM applies Equation (3.33) to find the concentration as function of position and time. Once the concentration is known, the flux (particles/s) can be found by extracting concentration values by using rakes and Equations (3.5) and (3.6). If a rake is not capable of getting accurate concentrations near surfaces, as in complex models, the particle fluxes are output for each of the boundary condition surfaces of the model. The deposition efficiency can be determined from the ratio of the particles entering through the inlet to the particles depositing on the wall, using Equations (3.8-10).

### 3.3.2 Grid Convergence Study

A grid convergence study was conducted on a straight tube having an alpha value of 1.0, which means the radius is equal in dimension to the length of the cylinder. The same boundary conditions were applied to the 3D cylinder as shown in Figure 3.1, however the axis has been moved. The \( C_0 \) concentration has been moved to the \( z=0 \), or \( \eta=0 \), plane and the \( z=l_0 \), or \( \eta=1 \), plane is set to \( C=0 \). The criteria used for determining a good mesh was satisfaction of the boundary conditions near the inlet (\( \eta=0 \)) and wall (\( \gamma=1 \)). The solution near these particular locations is of utmost importance because they will be used for calculating particle deposition.
and deposition efficiency. Figure 3.11 shows how each of the boundary conditions were applied
to the straight cylinder.

Meshes having a uniform grid spacing of 0.1 (4,000 elements), 0.05 (32,000 elements), and 0.025 (256,000 elements) were each created using GAMBIT, and steady solutions were solved for using FPM. The concentrations exported from the FPM solution were all normalized by the inlet concentration, $C_0$, and axial and radial dimensions were normalized by $l_0$ and $r_0$, respectively, as shown in Section 3.2. Concentration contours were created for rakes in the axial direction at a radial ($\gamma$) location of 0.98 (Figure 3.12 and Figure 3.13). In order to satisfy the boundary conditions, the rakes should show a value of 1.0 at $\eta=0$ and value of 0 at $\eta=1$. None of the uniform meshes were capable of satisfying these conditions at $\gamma=0.98$.  

![Figure 3.11: Boundary conditions applied to the straight cylinder in FPM.](image-url)
Figure 3.12: Normalized concentration contours shown for various grid spacing’s, each at $\gamma = 0.98$ and spanning from the model inlet to the end wall.

Figure 3.13 helps to better show the concentration contours by zooming in near the region of the inlet, since it is apparent that grid spacing has little effect on the solution after approximately $\eta = 0.15$.

Figure 3.13: Expanded view of same concentration contours as Figure 3.12 near the model inlet to help illustrate each individual grid spacing contour. It is shown that no grid spacing of 0.025 and higher is capable of matching the desired boundary condition.
An additional set of rakes was taken closer to the wall at the axial location of $\gamma = 0.99$ and concentration contours were plotted for each of the meshes (Figure 3.14 and Figure 3.15). Again, the results showed the uniform grid spacing’s incapable of matching the boundary condition at $\eta=0$.

![Concentration Contours at $\gamma = 0.99$](image)

**Figure 3.14:** Normalized concentration contours are shown for decreasing grid spacing’s. Each contour was taken along the axial rake of $\gamma = 0.99$.

Once again, the contours are shown to be unaffected by grid spacing after $\eta=0.15$, Figure 3.15 helps to better show the contours near the inlet. Not shown, grid spacing was decreased to a value of 0.01316 (1/76$^{th}$) creating a mesh with 1,316,928 elements, which approached the maximum number of elements that could be simulated due to computer restrictions, however, the results still did not agree with the boundary conditions at a rake of $\gamma = 0.99$. 

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A boundary layer was used in order to reduce the number of elements and to improve the accuracy of the solution near the wall. Before a boundary layer could be implemented, it was necessary for the model to be decomposed into quarters, which allowed for a Cooper mesh to be applied. A boundary layer was applied to each end of the model, an initial cell height of 0.005 was grown 10 rows using a growth factor of 1.1958 from the outer radius towards the axis of the model. After application, the model was re-meshed using a grid spacing of 0.025. Similar to the uniform meshes, the boundary conditions were applied and the FPM was used to solve for a steady solution. The concentration contours for the solution can be seen in the above Figure 3.12-Figure 3.15 as depicted by the line titled “0.025 w/ BL”, which is shown to satisfy the boundary conditions at both $\gamma=0.98$ and $\gamma=0.99$.

In addition to concentration contours in the axial direction, concentration contours were also produced for the radial direction. Rakes from the center of the cylinder to the outer radius were created at $\eta=0.01$ and $\eta=0.02$ for each of the meshes, and the values of concentration were plotted. The boundary conditions needed to satisfy consisted of $\sigma=0$ at $\gamma=1$ and $\frac{\partial \sigma}{\partial \gamma}=0$ at $\gamma=0$. The uniform 0.025 mesh and 0.025 mesh with a boundary layer were each unsuccessful in
meeting the boundary condition requirements at $\eta=0.02$, and both failed at satisfying the $\sigma=0$ at $\gamma=1$ condition at $\eta=0.01$.

It was not until a second boundary layer was applied to the inlet in the axial direction of the cylinder, that the boundary conditions requirements were met at $\eta=0.01$. Again, an initial cell height of 0.005 was grown 10 rows using a growth factor of 1.1958 from the inlet of the cylinder. Continuing to use a 0.025 mesh with a radial and axial boundary layer produced desirable results and a final mesh of 256,000 elements and 262,441 nodes (Figure 3.20). The results for the 0.025 spaced mesh with two boundary layers are shown in the previous and following figures and are appropriately labeled as “0.025 w/ 2 BL”.

![Concentration Contours at $\eta = 0.02$](image)

**Figure 3.16: Radial concentration contours at a location of $\eta = 0.02$ for varying meshes.**

In the following section, this grid independent solution for a closed-end cylinder is compared to Chen analytical model for validation.

In conclusion, a grid-independent solution for diffusion in a closed-end tube was obtained in FPM for the grid shown in Figure 3.20. The validation of this solution with Chen is discussed in Section 3.4.
Figure 3.17: Improved view near the model wall of Figure 3.16 helps to show that a grid spacing smaller than 0.025 is needed in order to agree with the boundary condition.

Figure 3.18: Radial concentration contours, similar to Figure 3.16, but at a location of \( \eta = 0.01 \), which is closer to the model inlet in the axial direction. For a better representation of the boundary condition near the wall, look forward to Figure 3.19.
Figure 3.19: The importance of the second boundary layer, projected axially, in matching the boundary condition is shown. The single boundary layer, which is projected in the radial direction, is not helpful in improving the accuracy in the axial direction. The .025 mesh with two boundary layers was chosen for final comparison to the Chen model.

Figure 3.20: Quarter section of straight cylinder converged mesh showing boundary layer mesh at inlet (top of left and right squares) and wall (outer edge of left and right squares), as well as, hex-wedge on the model inlet face (top).
3.4 Validation of the Fine Particle Model (FPM)

The straight closed-end cylinder geometry created in Section 3.3 was used to validate the solution of the FPM with that of Chen’s analytical model. The validation of the FPM was performed in two separate steps, first the steady state solution was compared to the steady portion of the analytical model. Second, the unsteady state portion was added to the analytical model which was then compared with unsteady FPM solutions.

3.4.1 Steady State Solution

The steady state solution from the FPM grid convergence study was used to evaluate against the steady analytical model solution. The double boundary layer mesh (Figure 3.20) was solved iteratively using FPM until residuals were reduced to a value of 1e-10. The analytical model was solved using a 0.005 spacing (200 x 200), which was summed a total of 150 times, as explained in Section 3.2.1.1.

Axial rakes (along z-axis) at various radial positions were taken from each steady state solution and the values of concentration were compared (Figure 3.21). Great agreement is shown at each location throughout the length of the cylinder.

Figure 3.21: Excellent agreement is shown between the steady solutions of Chen and FPM. A series of axial rakes of normalized concentration values have been shown, where Chen solutions are the lines and FPM are the points. ($\gamma =$ Normalized Radial Position)
Although good agreement is found in the central location of the cylinder, results from the grid study have shown that the region closest to the wall can be inaccurate while the rest of the model shows results of no concern. It is the wall region that is of the most importance because the concentration gradient is calculated here, which is directly related to the flux at the wall. Figure 3.22 shows the normalized concentration values along two axial rakes in close proximity to the wall of the cylinder. Close agreement is shown in each of the rakes, which were used to calculate the concentration gradient at the wall in Figure 3.25.

Additional rakes were taken spanning from the center axis to the wall of the model at intervals along the axial direction. Again, the values for concentration were taken at each of the nodes along the rake and compared to the analytical solution along the same plane. Figure 3.23 shows the results from each of these comparisons, and verification of the boundary conditions. The rake along the inlet, \( \eta = 0 \), shows a constant value of 1, as desired. At the rake along \( \eta = 1 \), a constant value of 0 is shown to occur, again matching the boundary conditions. Last, the slopes \( (d\sigma/d\gamma) \) for each data set is shown to approach 0 at \( \gamma = 0 \).

Figure 3.22: Great agreement is also shown between Chen and FPM for axial rakes at the locations of \( \gamma = 0.98 \) and \( \gamma = 0.99 \). These two rakes are of particular importance because they will be used for the calculation of particle flux at the wall. (\( \gamma = \text{Normalized Radial Position} \))
Figure 3.23: A comparison of radial concentration contours is shown between Chen and FPM, which are taken at a series of axial locations along the model. The verification of the boundary conditions is easily represented here. (\(\eta\) = Normalized Axial Position)

It was important to ensure that results in close proximity to the model inlet were accurate between the analytical model and FPM. Instabilities were already shown to occur in the analytical solution in regions close to the inlet, and an additional boundary layer was necessary to extract the correct solutions for boundary conditions in FPM solution. Rakes for the two planes near the inlet are shown below in Figure 3.24. The steady analytical and FPM solution are in great agreement and show no signs of instability or inaccuracy near the wall.

Figure 3.24: Good agreement of the concentration contours is shown near the model inlet, these contours were used in calculating the model’s inlet flux. (\(\eta\) = Normalized Axial Position)
The normalized concentration gradients at the wall and inlet were compared for the analytical model and FPM. The concentration gradient at the wall was found as a function of the axial location ($\eta$) and the inlet concentration gradient was found as a function of radial location ($\gamma$) (Figure 3.25). Good correlation has been shown for each gradient, which would be expected based upon the accuracy of the concentration contour results found in regions close to each.

Based upon the results shown, it was determined that the FPM solution is valid and accurate under steady state conditions. The non-dimensional results shown can be applied to cases of similar boundary conditions if the geometry is known.

Figure 3.25: An evaluation of the concentration gradients at the wall ($d\sigma/d\gamma$) and inlet ($d\sigma/d\eta$) for solutions of Chen and FPM provides good results, as would be expected based upon the great agreement shown in Figure 3.22 and Figure 3.24.

3.4.2 Unsteady Solution

Unsteady solutions for Chen’s analytical model were used for validation of the unsteady solutions of FPM at three different points in time: 1, 3, and 5 seconds. Chen’s model is capable of producing solutions for discrete points in time because it does not build upon solutions from previous times.

The unsteady FPM solution is obtained iteratively and requires time stepping in order to produce accurate results. The boundary conditions were setup so that a constant concentration of
particles was being introduced at the inlet for all time, as shown in Figure 3.11. Using a time step of 0.1 seconds, the case file was solved for a total of 50 time steps. Each time step was solved iteratively until residuals fell below 1e-9.

Concentration contours were reviewed at each of the times for solutions of each of the models, similar to those shown in the steady comparisons. Good agreement was shown for all contours at each of the times chosen for the wall. However, at the inlet, the concentration contours were shown to vary between Chen and FPM (Figure 3.26 – 3.28). Ultimately, it is the concentration gradients that are of importance since it is these which are used in calculating particle flux (rates of particles entering and particles depositing).

![Unsteady Validation at Inlet (1 second)](image_url)

Figure 3.26: Unsteady concentration contours near the inlet at time = 1 second. ($\eta$ = Normalized Axial Position)
The concentration gradient along the wall has been plotted versus the axial position for solutions at 1, 3, and 5 seconds in Figure 3.29. Since the gradient rapidly approaches zero as $\eta$, only a small portion of the axial data is represented in the figure. The lines correspond to the solution
based upon normalized concentrations from Chen’s analytical model and the points represent the results from FPM. The solution from FPM is shown to agree very well with that from the analytical model at each of the chosen times.

![Unsteady Solution Validation at the Wall](image)

Figure 3.29: The concentration gradient along the wall is shown for three different unsteady times. The plot has been magnified in the axial direction since the gradient rapidly approaches 0 in all cases. Good agreement is shown in each of the cases.

Similarly, the concentration gradient at the model’s inlet was plotted as a function of radial position for the same points in time (Figure 3.30). The solutions from each of the models are shown to have similar trends; however, the values are not in direct agreement. The disagreement of the concentration gradients at the inlet is generated by the disagreement of concentration contours shown in Figure 3.26 – 3.28. At each of the points in time, the percent difference was found to be roughly 6% (4.2% at 1 second, 6.2% at 3 seconds, and 5.7% at 5 seconds) between FPM and analytical solutions.

Although some issues were found in the unsteady solution near the model inlet, the results did not cause concern with the accuracy of the FPM. Using the Chen model as a method of validation, the FPM was considered valid for unsteady solutions.
Figure 3.30: Concentration gradients at the inlet are shown for three unsteady points in time, a slight shift is noticed in all cases, which attributes to roughly a 6% difference between Chen and FPM.
4 Chapter 4 Model Creation

4.1 Cast Lungs of Human

The lungs from a healthy and emphysematous human cadaver each were cast based primarily on a procedure described in the literature (Phalen et al. 1973). The lungs were obtained from the RIT cadaver lab (Biosciences Dept.), each from an adult male of undisclosed health background. Our agreement with University of Rochester does not allow detailed knowledge of the cadaver health or any personal identifying history.

4.1.1 Healthy Human Lung Cast

Similar to the procedure explained by Phalen (1973), the tertiary bronchiole, located just proximal to the posterior and lateral basal sections of the lower lobe of the left healthy lung, was cannulated (Figure 4.1). The bronchiole was cannulated by using a 10 ml disposable pipette, which was epoxied into position with the lung. The bulb end was removed and a piece of ¼ inch diameter polyethylene tubing (MSC Direct Part # 74204801) was inserted and epoxied for structural support and to create a junction for connecting. The polyethylene tubing provided a great seal with the 3/8 inch diameter Tygon tubing (MSC Direct Part # 79814620) that was connected to the CO2 tank regulator.

CO2 gas was used to inflate and deflate the lungs numerous times until a desired effect had been achieved. The cycling was dual purpose; first, since the cadaver had been fixed with preservatives, inflation was desired in an attempt to revitalize the lung’s elastic properties, which was slightly effective. Second, the CO2 was cycled in an attempt to remove and replace any air.

Figure 4.1: Illustration of medial view of left lung with detailed labeling of lobes (Netter 1979). Red circles show the lobes that were casted in the healthy human lung.
that was previously in the lungs. Some elasticity was shown to return after a number of full inflations of CO₂; it was not expected that all gas be exhaled by the lung’s elasticity alone. The lungs typically return to FRC after inhalation, which is similar to our observations. Additional compression to the lobes was required to completely exhaust all gases inside. Once it was comfortable that the lungs no longer contained air from atmosphere and were filled solely with CO₂, approximately 80 ml of saline was instilled into the lobes using a systolic pump at a flow rate of 80 ml/hr. It is important to note that an immeasurable volume of saline diffused out of the lung’s membrane during the instillation process. The properties of saline allow it to absorb the CO₂, as well as, be capable of diffusing through the lungs when a positive pressure is applied. By removing all of the CO₂, the intention was to create a lung cast with no bubbles that otherwise would be trapped in the casting material.

Next, the saline was displaced with the casting material, Dow Corning 3110 RTV, which was mixed with Dow Corning S Catalyst at a ratio of 20:1 (RTV to Catalyst based upon mass). This ratio correlates to the maximum working time of 3 hours, as per Dow Corning. A series of 140 ml syringes, which had been adapted for this procedure, were filled with 3110 RTV mixture. The luer lock tip of the syringe was removed to allow the least resistance by using a ¼ inch drill. After drilling, a piece of 3/8 inch diameter Tygon tubing was epoxied over the syringe’s tip, the same tubing as connected to the CO₂ regulator used prior. After securing the Tygon tubing to the polyethylene tubing using a zip tie, a KD Scientific KDS210 syringe pump was used for the first hour of instillation, which was when the force necessary to continue became too great for the pump. The total volume of 3110 RTV inside of the lungs was determined to be approximately 10 ml, based upon the KDS210 read out. After waiting one week to allow the material to cure, the lungs were introduced to a 4M NaOH solution to dissolve all the surrounding lung tissue. To help speed the process, large portions of the lung were removed that did not contain casting material. By doing so, it allowed the NaOH
solution to work effectively on the desired portion only. The NaOH solution was removed with any dissolved tissue and routinely replenished with fresh solution (Figure 4.3) until finally a complex airway structure remained (Figure 4.2).

![Image](image.png)

**Figure 4.3:** Series of digital pictures (labeled with timed intervals in base) starting with original healthy human lung to the final lung cast. The white circle in Original shows the airway that was cannulated.

### 4.1.2 Emphysema Human Cast

The emphysema lung was cannulated in two locations, so that two casts could be created after decomposition of the tissue had been completed. Since the entire lung must be dissolved to release the cast, the upper anterior and lower superior lobes (Figure 4.1) of the left lung were cannulated to insure that at least a single piece of interest would be created. Unlike the healthy lung, the availability of another emphysemic lung was not present, therefore extra caution was taken to insure that a successful cast would be created.
The same procedure as discussed to cast the healthy human lung was used for each emphysema lobe, however, some changes existed in the volumes of saline and 3110 RTV that were infused. A volume of 80 ml of saline and a volume of 60 ml of 3110 RTV was pumped into each of the lobes. The method for infusion of RTV into the lungs was improved, allowing for larger volumes to be injected. Previously a syringe pump was used, which only allowed for a maximum of 40 lbs of linear force to be applied. The syringe pump was desirable because of its accuracy in volume; however the force limitations were far too great. It was assumed the volume of the emphysema lobe be much larger than that of the human. Based upon the volume at which saline began to diffuse through the lung membrane as an estimate to TLC, the volume of 60 ml was chosen. A caulk gun and syringe were slightly modified to fit each other and allowed for the additional volume of RTV to be injected. Using a standard caulk gun, mechanical advantages of 20:1 (force exerted to force applied) or greater were easily achieved. The casting procedure for the second lobe was performed three days after the first lobe to help eliminate any unnatural features that may occur in the cast during the handling and the expanding and contracting.

To allow evaporation of the fixing agent, a wait of seven days took place before introducing the emphysema lung cast into the 4M NaOH solution for decomposition. Again, the solution was
replaced and deteriorated tissue was removed on a regular basis. After a month of this process, a cast for each of the lobes was exposed (Figure 4.5).

![Image of lung casts showing periodic progress of emphysema](image)

**Figure 4.5:** Digital pictures showing the periodic progress of emphysema human lung casts. The plastic inlet tube diameter (circled in each image) is 0.375 inches for reference to size of the casts.

### 4.2 Selection by Microscope and SEM of Desired Location

#### 4.2.1 Healthy Lung

After casting, three pieces of the healthy lung cast were removed (shown in Figure 4.6) to be examined under a high powered microscope to help locate regions of particular interest. Regions of interest were chosen based upon alveolar size, shape, completeness, presence of an inlet duct, and absence of air bubbles.
A Scanning Electron Micrograph (SEM) was later used to obtain photos containing a better depth of field and further magnification.

Unfortunately, the size constraints for nano CT scanning are that the sample must not be larger than 1 millimeter in any single direction. While reviewing these samples under the high powered microscope, it was determined that a nano CT scan of the samples would not prove to be beneficial (Figure 4.7). Due to the size constraints, it would only allow a few alveoli to be scanned and reconstructed. This is mainly due to the fact that human alveoli are 250 um in diameter (Haefeli-Bleuer and Weibel 1988). SEM pictures were taken for each of the three pieces as they were cut from the original cast (Figure 4.8). The quality of the healthy lung cast pieces were thought to be a good representation of the acinus region based upon illustrations and photos from previous literature, as well as expectations. During the casting procedure, the inside of the lung was examined and was filled with extremely dense, sponge-like tissue making up millions of very small air sacs. Although the morphology of this region of the lung is not well understood, it was felt that all measures
were taken during casting in order to properly recreate it. Piece 2 was finally chosen for continued analysis and reconstruction.

Figure 4.8: SEM photographs of each of the three pieces, (A) Piece 1, (B) Piece 2, and (C) Piece 3, trimmed from the healthy human lung cast.

### 4.2.2 Emphysema Lung

Two larger pieces were removed from the emphysema lung cast for further observation (Figure 4.9) under a high powered microscope. A first examination showed the alveolar sacs to be much larger in size, and lack of definition in comparison to the healthy cast (Figure 4.10). Although the emphysema casts showed these features, this was expected based upon observations during casting. The emphysema lung prior to casting showed extreme signs of tissue degradation and very large air sacs. This is portrayed in the lung casts and helps to prove the quality of the emphysemic casts in representing the actual diseased lung.

Figure 4.9: (A) Digital picture of the upper anterior lobe of the emphysema lung cast. (B) Zoomed in location of where the two emphysemic lung cast pieces were removed from (white circles). The white box in (A) illustrates the region that is zoomed in on in (B).
Using similar criterion as for the healthy lung piece of alveolar size, shape, completeness, and absence of air bubbles, the second emphysematous piece was chosen for reconstruction and analysis (shown in Figure 4.10).

4.3 CT Scanning of desired location

Computed tomography (CT) or computed axial tomography (CAT) is a medical imaging method employing tomography created by computer processing, whereby tomography is imaging by sections or section, through the use of wave energy (Hanks 2009). In the past 20 years, CT scanning has become increasingly popular in medicine, as well as, in nondestructive material testing.

CT scanning was implemented in order to generate a series of two-dimensional (2D) axial digital images for each of the chosen healthy and emphysematous lung cast pieces. From the series of images, a three dimensional (3D) digital reconstruction can take place, which can be used in various computer software packages.

4.3.1 Vendor Selection

During earlier research, micro CT scans of a healthy 12 week old C57BL/6J female mouse lung cast were performed at SUNY Upstate Medical University (Syracuse, NY) which was performed by an in vivo micro CT scanner. After in depth looks at the scan slices that were created, some doubt existed as to the quality of the resolution that would be received after digitally reconstructing the lung model. A human alveolus is roughly 250 µm in size and SUNY Upstate’s scan resolution is limited to a minimum of 37 µm per pixel, causing further research into other vendors and the discovery of high resolution micro CT scanning (Table 4.1). In vivo micro CT scanners are unable to get the same resolution due to the time required for scanning, it is not recommended to subject the live specimens to the increased amount of radiation that is required. Based on Table 4.1, the High Resolution micro CT scanning capabilities of Micro Photonics (Allentown, PA) were chosen for the healthy and emphysematous human lung casts.
The deciding factor between the vendors, Micro Photonics and Scanco Medical, was time for delivery/completion, experience with scanning similar samples, and capabilities of future nano CT scanning.

Table 4.1: CT vendors considered and their scanning capabilities.

<table>
<thead>
<tr>
<th>Vendor</th>
<th>SUNY Upstate</th>
<th>Micro Photonics</th>
<th>Micro Photonics</th>
<th>Scanco Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro/Nano</td>
<td>In vivo Micro</td>
<td>High Resolution Micro</td>
<td>High Resolution Nano</td>
<td>High Resolution Micro</td>
</tr>
<tr>
<td>Rates</td>
<td>$258</td>
<td>$400-1000</td>
<td>$1,200</td>
<td>$350</td>
</tr>
<tr>
<td>Resolution (microns/pixel)</td>
<td>37</td>
<td>3 to 8</td>
<td>0.4-0.7</td>
<td>6</td>
</tr>
<tr>
<td>Image Size</td>
<td>3072 x 2048</td>
<td>2k x 2k - 4k x 4k</td>
<td>1280 x 1280</td>
<td>512 x 512 - 4096 x 4096</td>
</tr>
<tr>
<td>Image Format</td>
<td>16 bit RAW</td>
<td>8 bit Bitmap</td>
<td>8 bit Bitmap</td>
<td>n/a</td>
</tr>
<tr>
<td>Scan Dimensions</td>
<td>8 cm (axial) x 5.4 cm (transaxial)</td>
<td>10mm - 78mm diameter (width)</td>
<td>1mm max. diameter</td>
<td>8 mm max. diameter</td>
</tr>
<tr>
<td></td>
<td>5.4 cm (axial) x 8 cm (transaxial)</td>
<td>155mm diameter (height)</td>
<td>5 mm max. height</td>
<td>140 mm max. length</td>
</tr>
</tbody>
</table>

4.3.2 Image and Scan Results

The two selected pieces of the healthy and emphysema lung casts were sent to Micro Photonics for micro CT scanning.

The healthy piece of roughly 6 mm in size was micro CT scanned at two resolutions. The first scan resolution was 1.79 µm/pixel, this resulted in a total of 2,294 slices. Each slice was a 2680 x 2680 pixel 8 bit bitmap image, which had a file size of 7,016 KB. The second scan resolution, twice the first, was 3.58 µm/pixel and created 1,241 slices. The file size was reduced to 3908 KB for each of the 2000 x 2000 pixel images.

The emphysema piece was micro CT scanned at only a single resolution of 3.35 um/pixel. The scan of the 12 mm piece produced 3,550 images, each a 4000 x 4000 pixel 8 bit bitmap picture. The file size for each image was 15,267 KB.

The effects of emphysema can easily be observed when comparing the cross section images of the healthy and emphysema lung casts (Figure 4.11). Each slice is at nearly the same micron/pixel resolution (3.58 vs. 3.35), however the emphysema slices contain twice as many
pixels in each direction (2,000 vs. 4,000). It is very evident that individual alveolar walls break down and the sacs merge into larger air spaces.

4.4 Reconstruction of Slices in 3D Doctor

The 3D Doctor software package, created by Able Software Corp., is an advanced 3D modeling, reconstruction, image processing and measurement software for MRI, CT, microscopy, scientific and many other medical and industrial imaging applications. 3D Doctor allows the choice between three different segmentation techniques: manual tracing, edge based segmentation, thresholding and region growing. After all the images have been segmented, 3-D surface or solid files can be created to be used for surgical planning, simulation, quantitative analysis, finite element analysis (FEA) and rapid prototyping applications.

4.4.1 Interactive Segmentation

The thresholding segmentation technique was chosen based upon the research provided in Jackie Russo’s thesis (Russo and Robinson 2007). After a region of interest was setup for the image set, the interactive segmentation feature allowed for all slices in the series to be segmented at one
time. The segmentation option of ‘Outline Only’ was necessary to eliminate the creation of inaccurate internal surfaces (Figure 4.12).

![Figure 4.12: 3D Doctor screenshots of two options (A) ‘All Boundary Lines’ and (B) ‘Outline only’ that can be selected during interactive segmentation. The image shown is a slice from the emphysemic human cast.](image)

After a small study, it was determined that thresholding values between the limits of 45 and 255 provided the most optimal results, as it included the largest majority of the cast surface without including too much of the surrounding static. These limits were used throughout the rest of the reconstruction procedure.

### 4.4.2 Simple Surface Rendering

After all images were segmented based upon thresholding, the simple surface rendering tool was used to stack the images and create a 3-D surface. Before this process can take place, it is required to input the pixel dimensions (length, width, thickness between slices) so that the program knows the voxel (pixel³) dimension. This ensures the rendering stacks the images to the same scale and accuracy. In our case the distance between slices was the same as the pixel length and width, therefore, no changes were necessary.

In order to look at the effects of the reconstruction a 3D editing software program, VP Sculpt, was used. VP Sculpt is a computer aided sculpting software package created by Colorado State, which allows editing, reshaping, and repairing of the model’s surface or to individual facets.
Some features of the program include smoothing, decimating, refining, filling holes, and removing improper facets.

4.4.3 1.79 vs. 3.58 µm/pixel resolution scans

The 1.79 µm resolution healthy scan (Figure 4.13A) appeared to be picking up crater like pits in the alveoli (shown in Figure 4.13C) that were not present during views of the cast under a high powered microscope or SEM. Whereas the 3.58 µm resolution healthy scan appeared to show the scan planes (horizontal lines across the entire scan), as shown in Figure 4.13D. However, the major features of the alveolar shape are captured adequately in the 3.58 µm resolution healthy scan (Figure 4.13B).

Figure 4.13: VP Sculpt screen shots of the reconstructions using the (A) 1.79 micron/pixel scan (top 500 images) and (B) 3.58 micron/pixel scan (all images) of the healthy model. (C) Zoomed in view of 1.79 micron/pixel scan to illustrate pits in the surface. (D) Zoomed in view of 3.58 micron/pixel scan showing the horizontal scan planes.
The disadvantage of the 1.7 µm healthy scan is that the number of images exceeds the memory allocation in VP Sculpt so that it would be necessary to reconstruct the model in at least 5 or more sections (Table 4.2 shows the details). The 3.5 µm scan files were chosen for the healthy model because they could be reconstructed all together as a whole and all of the desired features were accurately captured.

Table 4.2: Reconstructions of the healthy model performed to determine optimal scan resolution.

<table>
<thead>
<tr>
<th>Scan (micron/pixel)</th>
<th>Included Slices</th>
<th>Nodes</th>
<th>Triangles</th>
<th>Opens in VP Sculpt?</th>
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<tr>
<td>1.7</td>
<td>All</td>
<td>8,011,235</td>
<td>16,062,990</td>
<td>No</td>
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<tr>
<td>1.7</td>
<td>Bottom 500 (1989-2488)</td>
<td>2,262,058</td>
<td>4,538,955</td>
<td>Yes</td>
</tr>
<tr>
<td>1.7</td>
<td>Bottom 1000 (1489-2488)</td>
<td>9,566,269</td>
<td>19,941,612</td>
<td>No</td>
</tr>
<tr>
<td>1.7</td>
<td>Middle 500 (1488-1988)</td>
<td>5,615,533</td>
<td>11,488,549</td>
<td>No</td>
</tr>
<tr>
<td>1.7</td>
<td>Middle 250 (1739-1988)</td>
<td>2,918,434</td>
<td>5,950,428</td>
<td>Yes</td>
</tr>
<tr>
<td>1.7</td>
<td>Middle 250 2 (1489-1738)</td>
<td>2,697,097</td>
<td>5,536,585</td>
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<td>1.7</td>
<td>Top 500 (197-696)</td>
<td>1,270,474</td>
<td>2,539,475</td>
<td>Yes</td>
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<td>1.7</td>
<td>Middle 250 (697-946)</td>
<td>2,640,542</td>
<td>5,327,977</td>
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<td>3.5</td>
<td>All (29-1289)</td>
<td>3,759,282</td>
<td>7,516,779</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Upon completion of the preliminary segmentation and simple surface rendering of the healthy human set of slices, it was noticed that some additional noise or static was present in the images close to the edges of the cast (shown in Figure 4.13). Additionally, the presence of small air bubbles close to the surface was also causing some inaccuracies in the rendered model. It was determined that some additional image processing would be necessary to obtain a high quality final healthy model.

The preliminary reconstruction of the healthy model was compared to SEM photographs in order to obtain the orientation of the slices, and to further pinpoint a region of interest. The region was selected based upon criteria similar to SEM selection (absence of foreign material, complete alveolar shape, no air bubbles). The portion selected is highlighted with a white circle in Figure 4.14A, which eliminated the bottom 230 images from the scan (bottom referring to bottom of the model) reducing the total number of images for further image cleanup to 492. Only this region would be further processed and cleaned, while the other portions present in the image would be deleted.
A preliminary reconstruction was also performed using the top 1,016 slices from the emphysema lung cast, which again showed evidence of air bubbles and surface impurities. Using the reconstruction as a basis to determine orientation of the scan axis, a region was chosen for further image processing (shown in Figure 4.14B). The number of images that were necessary for processing was reduced to 919.

Figure 4.14: (A) The full reconstruction of all 1,261 slices of the healthy 3.58 micron/pixel scan resolution in VP Sculpt. The white circle shows the region chosen for further image processing and region of the final healthy model. (B) A reconstruction of the top 1,1016 slices of the emphysemic cast scan in VP Sculpt. The white circle shows the region chosen for further image processing and region of the final emphysemic model.

4.5 Refine and improve region by image processing in ImageJ

4.5.1 Section Removal

A procedure was adapted after a number of different image processing test trials, consisting of continuous segmentations and reconstructions. The final procedure consisted of using ImageJ, an image processing and analysis package developed by the National Institute of Health, to open the original scanned slices. Using the preliminary reconstruction for orientation, portions of the image were deleted leaving only the region of interest (Figure 4.15). This procedure was performed on the healthy and emphysemic sets of scanned images.
After all unnecessary sections were removed, the images were edited to remove features that are not consistent to \textit{in vivo}, such as filling in air bubbles near the cast’s surface (shown in Figure 4.16).

After all unnecessary sections were removed, the images were edited to remove features that are not consistent to \textit{in vivo}, such as filling in air bubbles near the cast’s surface (shown in Figure 4.16).

Figure 4.15: ImageJ was used to delete sections of the photo that were not in our region of interest. This would be beneficial for further reconstructions and reduces the number of nodes and faces. It is shown the section highlighted in white has been removed. The images shown are from the healthy scan.

Figure 4.16: Holes and air bubbles were filled in to accurately depict the acinus model during reconstruction. The improvements are shown above by looking at the two portions circled in white. Again, a set of healthy scan images is shown.

4.5.2 Static Cleanup

Unfortunately, after removing the unnecessary portions and filling in holes and air bubbles, some additional editing still remained which included reducing the halo and static near the cast’s
surface. It is visible in Figure 4.17 the effects this static has on the reconstructed model’s surface and exterior. To help reduce the effects of this unexplained static it was removed in order to make a more pronounced boundary between the image background and the lung cast cross section. The procedure for removing this halo included taking a small circle from the image background, copying, and then pasting it multiple times along the boundary. Particular care was taken so that the boundary did not change, which insured that no unnatural features would be added during reconstruction. As was done previously in the Section Removal, this procedure was performed on both the healthy and emphysema slices.

![Figure 4.17: A VP Sculpt screenshot of the emphysemic reconstruction showing the effects of image static on the reconstructed model’s surface, which led to the decision of additional editing to clean and remove it from the images.](image)
4.5.3 Final Model

The final healthy model reconstruction consisted of 368,238 nodes and 736,416 faces after all static cleanup had been performed on the slices, while the emphysema final model had 1,589,498 nodes and 3,174,083 faces. Figure 4.18 shows the final reconstructions of the healthy model and the emphysema model in VP Sculpt and how they compare to the actual lung casts. It is important to note that the microscope picture of the emphysemic cast has been mirrored due to the image capture device.

Figure 4.18: The final reconstruction in VP Sculpt of the healthy human model (top left) and emphysema human model (top right) are shown in good comparison to the healthy human lung cast SEM image (bottom left) and high powered microscope emphysema human lung cast image(botttom right).
4.6 Geometry Cleanup

4.6.1 Import OBJ to VP Sculpt

After reconstructions took place in 3D Doctor, object files, or .OBJ files, were created for each of the models and exported to allow an easy transition into VP Sculpt. The first step to cleaning the models’ surfaces was a series of smoothing operations; each model was smoothed roughly 50 times to eliminate any outlying features. The process of smoothing does not remove or add to the number of faces or nodes that make up the model’s surface.

Next, decimation took place on each of the models. Decimation is the combining of similar faces to create larger faces, thereby reducing the model size without losing detail to the surface. It was necessary to decimate the models four times before the size was reduced enough for importing to SolidWorks. The healthy human model was reduced to 27,012 nodes and 54,032 faces after decimating, while the emphysemic human model was left to 23,497 nodes and 46,982 faces.

The last step that was required before a duct could be added was to remove any improper, null, and appended facets and the bow tie and unconnected vertices that may have existed from the reconstruction or were created during the smoothing and decimation processes. In addition to removing these features, outer boundaries and holes were filled in order to produce a complete volume. Figure 4.19 shows the completed models in VP Sculpt after all processing had taken place and were ready for SolidWorks. Each model was exported from VP Sculpt as a stereolithography, or .STL, file for compatibility with SolidWorks.
Addition of Inlet Duct (Healthy and Emphysema) and Alveoli (Emphysema)

SolidWorks, a 3D mechanical CAD software package, was used to create the inlet ducts of the healthy and emphysemic models, as well as, completing the additional alveolar shapes of the emphysema model.

4.7.1 SolidWorks Additions

A procedure for creating the inlet ducts of the healthy and emphysema model was developed by making use of the built in tools from SolidWorks. After importing the .STL file as a Surface Body, the first step necessary was to choose a location from which the duct would extrude. A relatively flat region of the healthy model was found to be present and was chosen for the duct location (white circle in Figure 4.19A). Using points in the flat region to create a plane, the “Offset Entities” tool was used to create a profile. The profile was lofted to create a transition region between the duct and acinus. Next, a cylinder was extruded in opposite directions, above and below the plane previously created. The last step to creating the duct was to perform a series of lofts and extrudes in order to fill in, or smooth, the new addition to the acinus so that inaccuracies were not present during future analyses (Figure 4.20).
In addition to a duct, the emphysema model required alveolar features to be created in flat regions. These features were generated in a manner similar to the duct. A series of planes were created starting at the flat regions (white circles in Figure 4.19B) and progressing away from the model. Using “Offset Entities”, profiles were formed on each plane in order to form a spherical cap for each flat in the model (Figure 4.22).

The final step in SolidWorks was to export the newly created duct and alveolar region as a .STL file so that the additional features and acinus model could be merged together using VP Sculpt. Although the images in Figure 4.20 may show the duct and acinus together, the additional features are not connected to the acinus model when created in SolidWorks. The acinus is only imported so that it can be used as a template or aide for scale and orientation in creating the duct.

4.7.2 Import STL of Additions into VP Sculpt

VP Sculpt is needed for the combining of the duct created in SolidWorks to the cleaned up acinus created in VP Sculpt. Before the two models could be merged, the duct had to be translated to the same location as it was created in SolidWorks (Figure 4.21).
Unfortunately, after the duct was moved into its correct place the process was not complete, a problem occurred where the features intersect. If the two models were merged immediately, the faces that intersect were not removed and remained inside the model (Figure 4.22). This does not pose to be a problem immediately; however, when it was necessary to mesh the model in the future, the internal faces caused negative volumes that did not allow for simulating to take place. The reason for this is that each model is a surface geometry and is made up of surface nodes and faces only. It is easiest to think of the models as being hollow.

Figure 4.21: VP Sculpt screenshot shows the .STL file of the duct is not located properly with the acinus. The (A) before and (B) after images of translating the duct into the proper position are shown.
A procedure was developed for fixing this problem by removing the intersecting faces before the models are merged. For the healthy model, after the duct was moved to its correct place, the “Trim Model at Intersection” feature in VP Sculpt was used on the duct and acinus piece, separately. The two trimmed models were then opened together and merged, however a large hole, or gap, was still present in the newly merged model that needed to be taken care of (Figure 4.23). It was necessary to create additional facets around the duct and acinus to gap the distance between the two models before the “Fill All Holes” feature performed the desired operations.

Figure 4.22: VP Sculpt screenshots showing how intersecting faces are not removed after two models have been merged. The white circles highlight regions where internal faces occur after the duct and alveolar features have been merged to the models by showing a cross section view of the (top row) healthy and (bottom row) emphysema models.
A similar procedure was performed for merging the duct and additional alveolar features on the emphysema human model. The final models after all merging and cleanup had been performed are shown in Figure 4.24.

Figure 4.23: The gap that remains after merging the trimmed duct and alveolar model is shown in VP Sculpt. The upper left corner is used to shown the region which is zoomed in upon.

Figure 4.24: (A) The completed healthy model is shown after the duct has been added and surface has been cleaned. (B) The final emphysemic model is shown with additional alveolar features and duct. (Both images are screenshots from VP Sculpt)
4.7.3 Model Scaling

One final step was necessary before meshing could take place, the models needed to be scaled correctly to accurately depict in vivo dimensions. Up until this point an arbitrary unit of measure had been used that was produced when the model was reconstructed in 3D Doctor. The correct scaling factor was determined by making use of the SEM and high powered microscope pictures. The photos were analyzed using ImageJ, by using the scales present in each of the images an accurate length scale could be generated. For example, using the 1 mm scale in the SEM image of Figure 4.26, a millimeter to pixel conversion could be created and applied to other dimensions in the photograph.

The healthy reconstructed model was rotated into a position similar to the microscope photo and a single dimension was taken and compared for each (Figure 4.25). A scaling factor of 0.00361 was used in VP Sculpt to reduce the healthy model to in vivo size. After scaling the reconstructed model, a series of three additional measurements were compared between the reconstructed model and the SEM photo (Table 4.3).

Figure 4.25: (A) Microscope picture and (B) VP Sculpt screenshot used to obtain scaling factor from arbitrary dimensions to in vivo dimensions. The red lines in each image represent the location of the dimension which was compared.
Table 4.3: Comparison between ImageJ and VP Sculpt dimensions after scaling the healthy model by 0.00361.

<table>
<thead>
<tr>
<th>Length in ImageJ (mm)</th>
<th>Length in VP Sculpt (mm)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.247</td>
<td>0.252</td>
<td>2.03%</td>
</tr>
<tr>
<td>0.399</td>
<td>0.438</td>
<td>9.90%</td>
</tr>
<tr>
<td>0.425</td>
<td>0.425</td>
<td>0.08%</td>
</tr>
</tbody>
</table>

The model and photo showed good agreement; with the blue dimension having an average difference of 0.08%, the green line having an average percent difference of 2.03%, and the red line had a slightly higher percent difference of 9.90% (Figure 4.26). However, it can be seen that for the red line the right side begins to move out of the depth of the field, which could explain the higher difference.

The scaling factor that was used in the emphysema model was 0.00306, and was obtain using the same procedure that was performed in the healthy model. Again, good agreement was found when comparing additional dimensions after scaling; having percent differences of 1.02%, 2.02%, and 13.28% (Figure 4.27 and Table 4.4).

Figure 4.26: SEM photograph of healthy cast used for comparing 3D model scaling to actual lung cast. The colored lines represent different dimensions that were used for comparing.
Table 4.4: Comparison between ImageJ and VP Sculpt dimensions after scaling the emphysemic model by 0.00306.

<table>
<thead>
<tr>
<th>Length in ImageJ (mm)</th>
<th>Length in VP Sculpt (mm)</th>
<th>% Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.984</td>
<td>0.974</td>
<td>1.02%</td>
</tr>
<tr>
<td>2.293</td>
<td>1.988</td>
<td>13.28%</td>
</tr>
<tr>
<td>1.686</td>
<td>1.652</td>
<td>2.02%</td>
</tr>
</tbody>
</table>

Similar to editing the acinus, the final models were cleaned by removing improper facets, etc. before exporting .STL files for meshing in Harpoon.

4.8 Mesh

Harpoon (Sharc Ltd, Manchester, England) is an automatic hex dominant volume meshing software tool which is capable of meshing complex geometries that other mesh tools commonly struggle with. Due to the use of hexagonal elements, convergence and solver time are drastically reduced making this product a great choice for this application.
4.8.1 Harpoon to create BC’s and mesh

A .STL file is imported into Harpoon as one complete surface, therefore, the first step before meshing was to break the single surface into two faces, the inlet and acinus wall. The models were separated by using the “Separate by…Feature” tool, but only after the Geometry Preferences Separation Angle had been set to 20. The inlet face was then located and labeled properly; the remaining faces were merged together to created the acinus wall. Meshing of the models could now take place.

The mesh settings for Harpoon allow the user to control the surface cell size, maximum volume mesh size, mesh type, and mesh expansion (Figure 4.28). The surface cell size and maximum volume size are each functions of the Base Level. Using different settings can allow the mesh to contain elements all of the same size or a mesh that has smaller elements near the wall and larger elements in the center (Figure 4.29).

![Figure 4.28: Harpoon mesh settings panel](image)

**Figure 4.28: Harpoon mesh settings panel**
The healthy model was meshed using a Base Level of 0.04, a Surface Cell Size of Level 3 (0.01000), and Max Vol Size of Base Level (0.04000), which created 774,380 elements and 627,214 nodes. The Surface Cell Size is approximately 0.6% of the healthy model’s x, y, and z dimensions, similar to the initial boundary layer height being 0.5% of the radial and axial dimensions of the tube used in the Chen validation. The Max Vol Size is 2.4% on average of the model’s dimensions, which compares well with the internal mesh being 2.5% of the Chen tube’s dimensions.

Figure 4.29: Mesh effects of different settings in Harpoon to obtain a (A) uniform element size or (B) mesh with element size tighter along boundaries and coarser in the middle of the model.
The emphysemic model was meshed using a Base Level of 0.025, a Surface Cell Size of Level 2 (0.01250), or 0.4% of the model’s size, and Max Vol Size of Base Level (0.02500), or 0.7% of the overall size, which created 947,199 elements and 842,689 nodes.

After meshing, each mesh was exported as a surface and volume mesh designated for Fluent. The final Harpoon meshes are shown in Figure 4.30 and Figure 4.31.
4.9 Model Geometry

The healthy human model including the duct addition extends 2.11 mm in the x-direction, 1.34 mm in the y-direction, and 1.74 mm in the z-direction. The total volume of the model is only 1.16 mm$^3$, or 1.16e-3 ml. The inlet duct diameter measures 0.41 mm, which is well within the limits for a duct in this region of the lung. A series of human lung casts were measured which reported alveolar duct diameters on average to range from 0.25 to 0.50 mm in the acinus (Haefeli-Bleuer and Weibel 1988).

The emphysema model with the additional alveolar features and duct had a total volume of 12.49 mm$^3$, or 1.25e-2 ml. The emphysema model is 10.8 times larger than the healthy model by volume. The global size of the model measures 3.74 mm, 3.18 mm, and 3.49 mm in the x, y, and z directions, respectively. Last, the inlet duct of the emphysema model had a diameter of 0.81 mm. Kohlhaufl et al. (1988) reported an effective airway diameter (EAD) of 0.63 mm, however an EAD of 0.86 mm was reported by another one of his studies in 1998. The duct diameter of the emphysemic model falls between the values published.
5 Chapter 5 Results

5.1 CFD Parameter

The Fine Particle Model (FPM) add on to Fluent, previously discussed in Chapter 3 Theory, was used to solve the convective-diffusion equation (Equation (3.2)) on each mesh of the healthy and emphysemic models. A constant inlet concentration of $1e15$ particles/m$^3$ was set at each of the model’s inlets, while the walls were set to remain at a concentration of 0 particles/m$^3$. Two groups of particles, sizes of 1 nm and 3 nm, were analyzed for a period of 5 seconds by concentration contours, particle flux (Equations (3.5) and (3.6)), and particle deposition (Equations (3.8) and (3.9)) for each of the models.

Attempts to simulate larger particle sizes of 8, 10, 30, 100, and 300 nm were unsuccessful due to the residuals not converging properly which caused negative concentrations to exist inside the models in some of the cases.

5.2 Concentration Contours in Healthy and Emphysema Models

The unsteady concentration contours in the healthy model were all taken at a x-y plane located in the center of the inlet duct. The unsteady concentration contours shown below for the emphysema model are also located at the center of the inlet duct. Figure 5.1 shows the concentration contours for the 1 nm group of particles in the healthy (A, C, and E) and emphysematous (B, D, and F) models at three points in time during the simulation period. The first two times were chosen arbitrarily, while the last point in time (Figure 5.1(E and F)) was chosen to be steady state. No change was found to occur in the contours of the healthy model after about 0.08 seconds (Figure 5.1(E) and Figure 5.5). The concentration contours in the emphysemic model stopped changing after roughly 0.17 seconds (Figure 5.1(F) and Figure 5.6). It is important to note that the scale is consistent among each of the images and that regions showing blue simply mean the concentration is lower than the minimum value of the scale.

Figure 5.1(A and B) shows the concentration contours of the healthy and emphysema models at the same point in time early in the simulation. It is easy to see that the particles have been able to diffuse deeper into the healthy model over the same period of time. Figure 5.1(C and D) show
similar concentration contours, however, the simulation time of the emphysemic model is 6 times that of the healthy model, again displaying the increased diffusion time.

Figure 5.1: Concentration contours in the (A, C, and E) healthy and (B, D, and F) emphysematous models for three points in time of the 1 nm simulations. The healthy cross sections were taken at z=0.34 mm and the emphysemic cross sections were taken at z=-1.34 mm. (E) and (F) correspond to steady state in each case.
Figure 5.2 shows concentration contours for the 3 nm group of particles at three points in time for the healthy (A, C, and E) and emphysemic (B, D, and F) models. The healthy 3 nm concentration contours were found to have no changes after approximately 0.26 seconds (Figure 5.2(E)), while the emphysemic model took nearly 0.5 second Figure 5.2(F) before contours became steady.

An important finding can be seen when viewing the steady state healthy images (Figure 5.1(E) and Figure 5.2(E)) and the steady state emphysematous images (Figure 5.1(F) and Figure 5.2(F)). As expected, the steady state concentration contours are the same for each model even though the particle sizes that were released at the inlet were different. Looking back to Equation (3.2) in Chapter 3, at steady state the diffusion coefficient no longer contributes to the solution of the concentration. Therefore explaining why the concentration contours for any size particle will look the same at steady state. The total particle deposition, which is based up on particle flux, will not be the same for different particles due to the diffusion coefficient’s presence during calculations. Since steady state is reached relatively quickly in all cases, for further analyses only the steady state solution will be reviewed. The accuracy of this assumption is discussed in Section 5.7.

The healthy model has been broken down into six planes, spaced equally, 0.248 mm, throughout the z-axis (Figure 5.3). Plane #2 was located in the center of the duct. Similarly, the emphysemic model has been sectioned six times, 0.499 mm, over the span of the z-axis (Figure 5.4), with plane #6 located at the duct’s center. A better view of the steady state solution in the healthy model, showing the global distribution of concentration in each plane throughout the model, can be viewed in Figure 5.5. An isometric view of each of the planes combined is shown in Figure 5.7(A). Figure 5.6 shows the concentration contours in each of the six emphysemic planes, which are joined into a single isometric view in Figure 5.7(B).
Figure 5.2: Concentration contours in the (A, C, and E) healthy and (B, D, and F) emphysematous models for three points in time of the 3 nm simulations. The healthy cross sections were taken at $z=0.34$ mm and the emphysemic cross sections were taken at $z=-1.34$ mm. (E) and (F) correspond to steady state in each case.
Figure 5.3: (A) Isometric view and (B) top view of the six planar locations analyzed in the healthy model in Figure 5.5 and Figure 5.7. The distance between each plane is 0.248 mm, while the plane #2 is located at z=0.34 mm.

Figure 5.4: (A) Isometric view and (B) top view of the six planar locations analyzed in the emphysemic model in Figure 5.6 and Figure 5.7. The distance between each plane is 0.499 mm, while the plane #6 is located at z=−1.30 mm.
Figure 5.5: Contours showing the global distribution of concentration throughout the healthy model.
(Numbers correspond to the planes shown in Figure 5.3)
Figure 5.6: Contours showing the global distribution of concentration throughout the emphysematous model. (Numbers correspond to the planes shown in Figure 5.4)
Figure 5.7: Isometric views of the concentration contours for the equally spaced six planes in the (A) healthy and (B) emphysemic models.
5.3 Particle Flux in Healthy and Emphysema Models

The particle flux at the inlet and wall (Equations (3.5) and (3.6)) was calculated after the convective-diffusion equation had been solved based upon Equation (3.1), by summing over the area of the inlet or wall. The particle flux was analyzed using a custom user defined function (UDF) for Fluent and FPM, which was designed to automatically output the inlet and wall flux to a text file after each time step of the simulation. The UDF code can be found in Appendix A – UDF Code. The plots shown are based on this flux output. Note that since the wall flux originally is negative when output from FPM, because the particles are exiting the model and traveling in the direction opposite to the normal of the wall, they were made positive before plotting. For comparison purposes, the inlet concentrations for each model and each particle size were kept at 1e15 part/m³.

5.3.1 Healthy

The inlet and wall fluxes for both the 1 nm and 3 nm simulations are shown to converge very quickly upon one another (Figure 5.8). It is difficult to see but the inlet flux for the 1 nm solution starts at approximately 1.5E+08 particles/s, while the wall flux starts near 3.4E+06 particles/s. Each is shown to converge quickly to a value of 1.6E+07 particles/s. The 3 nm solution’s inlet flux starts around 2.0E+07 particles/s with the wall flux beginning at nearly 1.0E+05 particles/s. The fluxes for this solution quickly settle around 1.8E+06 particles/s. Figure 5.8 helps to view just how quickly the fluxes converge by showing the first 0.01 seconds of each healthy simulation.
Figure 5.8: Plot showing initial 0.01 seconds for the inlet and wall fluxes. The 1 nm and 3 nm simulation results have been combined and shown for the healthy model. The 1 nm inlet flux has been cut off in the beginning to help portray the overall trend of all of the lines. Inlet concentration of 1E+15 particles/m³.

5.3.2 Emphysema

Similar to the healthy solutions, the inlet and wall fluxes for the two emphysemic simulations have been shown for both the 1 nm and 3 nm cases in Figure 5.9. The inlet and wall fluxes for the group of 1 nm particles start near 3.7E+08 and 3.3E+06 particles/s, respectively, and progress towards the steady state flux of around 3.3E+07 particles/s. The 3 nm solution inlet and wall fluxes start off lower, possessing values of 4.6E+07 and 1.3E+04 particles/s, respectively. Each took slightly more time than the comparable healthy simulation to approach one another before reaching the final flux value of 3.7E+06 particles/s. Neither of the simulations has completely converged at this point in the simulation, but it’s quite apparent that it will occur shortly after based upon the shown trends.
5.4 Deposition in Healthy and Emphysema Models

The total particle deposition in the healthy and emphysemic models was obtained using the wall flux output and summing it over the period (Equation (3.8)). The measure of “total number of particles deposited” is typically used for inhaled medication (Figure 5.10), and is associated with the amount of translocation to the blood stream; however “particles per unit of surface area” is more commonly used for toxicity (Figure 5.11) since it is a representation of the toxic loading on the individual cells. The values in each of the figures vary only by the surface area of the model’s wall: 1.05E-05 m² for the healthy model and 3.36E-05 m² for the emphysemic model.
Figure 5.10: Plot showing the deposition of particles in the healthy and emphysemic models for particle sizes of 1 and 3 nm over a 5 second period.

Figure 5.11: Plot showing the deposition of particles per surface area in the healthy and emphysemic models for particle sizes of 1 and 3 nm over a 5 second period.
The percent deposition, or deposition efficiency, of particles was calculated by taking the ratio of the number of particles deposited over time (Figure 5.10) to the number of particles that entered over that time, as shown in Equation (3.10). Figure 5.12 displays the percent deposition for groups of 1 nm and 3 nm particles in the healthy and emphysemic models over a 2 second period. In both models, the 1 nm cases approaches steady state conditions before the 3 nm cases.

![Compare Deposition Efficiency for H and E Models](image)

Figure 5.12: Plot showing the percent deposition of particles entering the healthy and emphysemic models for particle sizes of 1 and 3 nm over a 2 second period, which shows the efficiencies to have converged to steady state.

### 5.5 Comparison to *in vivo* Pulmonary Deposition Data from the Literature

Although there is no experimental evidence for particle sizes analyzed in this study, some conclusions can be drawn based upon some of the past studies. Figure 5.13 shows all of the experimental data that was outlined in Section 2.6.

In order to compare our results to experimental data, we determined the pulmonary deposition from particles that entered the pulmonary region during the brief pause time between inhale and exhale. Table 5.1 gives the pause times, for a pause cycle fraction of 4.9%, for three breathing frequencies, and the local alveolar deposition fraction at those pause times, predicted from our model. These breathing frequencies were chosen to represent the range used for the *in vivo* deposition studies.
Furthermore, in order to compare these values to the \textit{in vivo} data, we must first account for filtering in the TB region. The particles depositing in the TB region never make it to alveolar region, and therefore must be removed from the total fraction of particles entering. To account for the TB filtering in the \textit{in vivo} data, it was necessary to determine the deposition fraction of the TB region so that this could be subtracted out of the deposition fraction that enters the alveolar region. After knowing the deposition fraction of particles entering the alveolar region, the new deposition fraction could be obtained by taking the ratio of the fraction of particles that deposited to the fraction of particles that entered. Figure 5.13 shows the local alveolar deposition fractions for the experimental \textit{in vivo} studies, along with the local alveolar deposition results from the healthy and emphysema simulations. Note that Stahlhufen et al. (1980) did not provide TB data and therefore is not included in Figure 5.13. It is difficult to draw any real conclusions from this data due to the large disconnect between particle sizes, perhaps additional studies using smaller particles could help contribute in the future.

![Figure 5.13: Plot showing the local alveolar deposition fraction vs. particle diameter for experimental \textit{in vivo} studies and the healthy and emphysema simulations. (Triangles, squares, and circles correspond to pause times of 0.294, 0.196, and 0.134 seconds, respectively, while black and orange correspond to healthy and emphysema, respectively.)](image-url)
Table 5.1: Pause times and local deposition fractions from this study at pause times for four breathing frequencies.

<table>
<thead>
<tr>
<th>Breathing Frequency (breaths/min)</th>
<th>Pause Time (sec)</th>
<th>Healthy 1 nm</th>
<th>Healthy 3 nm</th>
<th>Emphysema 1 nm</th>
<th>Emphysema 3 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.294</td>
<td>0.96</td>
<td>0.93</td>
<td>0.94</td>
<td>0.84</td>
</tr>
<tr>
<td>15</td>
<td>0.196</td>
<td>0.95</td>
<td>0.92</td>
<td>0.93</td>
<td>0.81</td>
</tr>
<tr>
<td>22</td>
<td>0.134</td>
<td>0.95</td>
<td>0.92</td>
<td>0.91</td>
<td>0.77</td>
</tr>
</tbody>
</table>

5.6 Comparison to Other Model Studies in Literature

As reviewed in Section 2.3, there are deposition models that have been developed for simulating the particle deposition in each generation of the lung based upon straight tube assumptions and average lung geometries. These models do not include closed-ended tubes or geometry similar to in vivo alveolar shapes, while others only look at deposition during inspiration. Using these deposition models, simulated particle deposition can be obtained for very small particles, similar to the scale in this study. As a method of validation, each model was compared against another, which showed good agreement.

The deposition fractions shown in Figure 2.10 are relative to the amount of inhaled particles. Similar to the in vivo experimental studies, these can be converted to local alveolar deposition fractions in order for the healthy and emphysema simulation results to be compared. For the MPPD model, deposition fractions from generations 1 through 13 were added together to account for deposition in the TB region of the lung. The remaining fraction of particles was assumed to enter the alveolar region. Deposition fractions for generations 14 through 24 were summed to obtain the alveolar deposition fraction. The ratio of the two deposition fractions, fraction of particles remaining to fraction of particles deposited, was considered to be the local alveolar deposition fraction. For example, for 0.005 μm particles, the sum of the MPPD model’s TB deposition fractions (1-13) were 0.1, the summed alveolar deposition fraction (14-24) was 0.44. Therefore, only 90% of the particles were able to reach the alveolar region. Therefore, the local alveolar deposition fraction becomes 0.44/0.9; a fraction of 0.55 or 55%. A similar
procedure was performed on the results output for the Trumpet model. Figure 5.14 shows the comparison of local alveolar deposition of the two whole lung models and the healthy and emphysema model at the three previously discussed pause times. Similar to the in vivo experimental results, there is very little agreement between the two models and our results.

Although these models have not been validated experimentally for nanoparticles, Scherer et al. (1972) presents two models, one analytical and one numerical, for N₂, which has a diameter on the same order of magnitude as our simulations. Scherer’s models were shown to have relatively good agreement with experimental results. The solutions from the MPPD and Trumpet models, shown in Figure 5.14, are based upon the theory of Scherer’s solutions.

The healthy and emphysema whole lung models presented in the work of Sturm and Hofmann (2004), showed similar trends in alveolar deposition as the Trumpet and MPPD models. The data shown in Figure 5.15 is for overall alveolar deposition, and not local alveolar deposition that has been shown thus far. It was determined that particle deposition was greater in the healthy lung model by approximately 7% when compared to the emphysema models. The trends of our
results agree with Sturm and Hofmann, which found the deposition efficiency in the healthy model to be 96% in both cases and in the emphysema to only be 93% and 94% for the 1 and 3 nm cases, respectively.

![Particle Deposition Plot](image)

Figure 5.15: Percent alveolar deposition results for healthy and emphysema whole lung models. (Sturm and Hofmann 2004)

### 5.7 Accuracy of Steady State Assumption

As previously discussed, the healthy simulations quickly approach steady state, which means the rate of deposition of particles with respect to time becomes constant after only a short period of time. This is evident in the particle deposition plots as they become nearly linear with respect to time very quickly. Assuming steady state deposition over the entire breathing period provides the opportunity to simplify the numerical simulations. Steady state was assumed to occur when the change in the deposition efficiency curve became less than 0.1% per second (Figure 5.16.)
Figure 5.16: Slopes of percent deposition curves from Figure 5.12. Red line shows the criterion used to determine when steady state has occurred.

Table 5.2: Criteria for reaching steady state based on different model results

<table>
<thead>
<tr>
<th>Steady State (SS) Values</th>
<th>1 nm</th>
<th>3 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy Emphysema</td>
<td>Healthy Emphysema</td>
</tr>
<tr>
<td>SS Deposition (%)</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>SS Time (s)</td>
<td>0.08</td>
<td>0.17</td>
</tr>
</tbody>
</table>

The time frame for each model to reach steady state is provided in Table 5.2. The 1 nm healthy simulation approached steady state at 0.08 sec. During this time, an unsteady solution predicts a deposition of 1.28E+06 particles, while the steady state solution (using the steady state wall flux of 1.64E+07 particles/s) predicts a deposition of 1.29E+06 particles, an increase of 6350 particles, or a 0.50% overestimation. Therefore, it is clear that the error associated with the steady state assumption is relatively small. If this over-estimation in 1 nm particle deposition is compared to the 1 nm particles deposited over 1 second (1.64E+07 particles) or 5 seconds (8.19E+07 particles), the total over-estimation is 0.04% and 0.01%, respectively. These values and the associated errors for the other 3 model cases are shown in Table 5.3. The worst case is
the 3 nm in E, which gives errors of 4.12% at the steady state time of 0.49 sec, and 1.98% and 0.39% at 1 and 5 seconds, respectively.

Table 5.3: Error introduced when assuming steady state for entire breathing period.

<table>
<thead>
<tr>
<th></th>
<th>Healthy (H)</th>
<th>Emphysema (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 nm</td>
<td>3 nm</td>
</tr>
<tr>
<td>SS time (seconds)</td>
<td>0.08</td>
<td>0.26</td>
</tr>
<tr>
<td>Unsteady Deposition</td>
<td>1.28E+06</td>
<td>4.69E+05</td>
</tr>
<tr>
<td>(Particles)</td>
<td>1.29E+06</td>
<td>4.75E+05</td>
</tr>
<tr>
<td>Deposition using</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steady State Assumption (Particles)</td>
<td>1.29E+06</td>
<td>4.75E+05</td>
</tr>
<tr>
<td>% Error at SS time</td>
<td>0.50%</td>
<td>1.46%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deposition at 1 second</td>
<td>1.64E+07</td>
<td>1.82E+06</td>
</tr>
<tr>
<td>% Error at 1 second</td>
<td>0.04%</td>
<td>0.38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deposition at 5 seconds</td>
<td>8.19E+07</td>
<td>9.14E+06</td>
</tr>
<tr>
<td>% Error at 5 seconds</td>
<td>0.01%</td>
<td>0.08%</td>
</tr>
</tbody>
</table>

If we assume that all pulmonary deposition takes place during the pause between inhalation and exhalation, it is of interest to determine what proportion of the pause is characterized by unsteady state deposition relative to steady state. To do this, we provide Table 5.4, which gives the fraction of unsteady state (change in deposition efficiency > 0.1% per second) to the total pause time for various breathing frequencies for a pause cycle fraction of 4.9%. It can be seen from Table 5.4 that steady state behavior dominates for all breathing frequencies of 1 nm healthy, but only 12 and 15 breaths/min for the 1 nm emphysema case. Unsteady behavior is 50% or more of the pause time for all 3 nm emphysema cases.
Table 5.4: Ratios of time to reach steady state to pause time for four breathing frequencies.

<table>
<thead>
<tr>
<th>Breathing Frequency (breaths/min)</th>
<th>Pause Time (sec)</th>
<th>1 nm</th>
<th></th>
<th>3 nm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Healthy</td>
<td>Emphysema</td>
<td>Healthy</td>
<td>Emphysema</td>
</tr>
<tr>
<td>12</td>
<td>0.25</td>
<td>0.32</td>
<td>0.69</td>
<td>1.06</td>
<td>2.00</td>
</tr>
<tr>
<td>15</td>
<td>0.20</td>
<td>0.40</td>
<td>0.87</td>
<td>1.33</td>
<td>2.50</td>
</tr>
<tr>
<td>20</td>
<td>0.15</td>
<td>0.53</td>
<td>1.16</td>
<td>1.77</td>
<td>3.33</td>
</tr>
<tr>
<td>22</td>
<td>0.13</td>
<td>0.59</td>
<td>1.27</td>
<td>1.95</td>
<td>3.67</td>
</tr>
</tbody>
</table>

5.8 Extrapolated Particle Deposition

It was previously demonstrated (Section 5.2) that the steady state concentration contours are independent of particle size. Therefore, the steady state concentration gradients found for the 1 and 3 nm particles, in this work, can be used to extrapolate steady state wall flux for any other size particle. The following calculation, demonstrates that theoretically, the steady state solution for the integral of div C over the surface area, is independent of particle size. Using Equation (3.5), this value can be solved for as follows:

For the 1 nm particle,

\[ J'_{wall} = -\int_{wall} D \nabla C \, dA \]

\[ \frac{1.64E+07 \text{ particles}}{s} = \left( \frac{5.32E-06 \text{ m}^2}{s} \right) \int_{wall} \nabla C \, dA \]

\[ \int_{wall} \nabla C \, dA = \frac{1.64E+07}{5.32E-06} = 3.08E+12 \frac{\text{particles}}{\text{m}^2} \]

where A is the wall area. And the same value is found for the 3 nm particle,

\[ J'_{wall} = -\int_{wall} D \nabla C \, dA \]

\[ \frac{1.83E+06 \text{ particles}}{s} = \left( \frac{5.94E-07 \text{ m}^2}{s} \right) \int_{wall} \nabla C \, dA \]

\[ \int_{wall} \nabla C \, dA = \frac{1.83E+06}{5.94E-07} = 3.08E+12 \frac{\text{particles}}{\text{m}^2} \]
The integral of \( \text{div} \ C \) over the area for the emphysema model was calculated (using the values shown in Table 5.5) to be 5.86E+12 particles/m\(^2\). Steady state deposition rates in the healthy and emphysema model can be found for other particle sizes by making use of Equation (3.5). Table 5.6 gives a range of particle sizes and the diffusion coefficients (D) for each. Figure 5.17 shows the resulting steady state deposition rates (particles/s) for various particles in both models by taking the corresponding \( \text{div} \ C \) integral and multiplying by the diffusion coefficient of different particles. If the deposition rate is known, then the total number of deposited particles can easily be obtained by integrating over the desired time period (Figure 5.18). Figure 5.19 shows the deposition rate per unit area in the healthy and emphysemic model by dividing by the wall area for each model.

Steady state deposition rates for the healthy and emphysemic models show a decreasing trend as particle sizes increases, as expected due to the particle’s diffusion coefficient become smaller as particle size increases. The deposition rate is shown to be greater in the emphysema model in comparison to the healthy model, which is likely due to the increase in alveolar wall surface area for the particles to deposit. After the area component is removed from the deposition rate values, the healthy deposition rate is greater than the emphysemic rate.

Table 5.5: Values used to calculate value of steady state concentration gradients for deposition extrapolation.

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 nm</td>
<td>3 nm</td>
</tr>
<tr>
<td><strong>SS Wall Flux - ( J'_{\text{wall}} )</strong> (Particles/s)</td>
<td>1.64E+07</td>
<td>1.83E+06</td>
</tr>
<tr>
<td><strong>Diffusion Coefficient - D</strong> (m(^2)/s)</td>
<td>5.32E-06</td>
<td>5.94E-07</td>
</tr>
<tr>
<td>( \int_{\text{wall}} \nabla C , dA ) (Particles/m(^2))</td>
<td>3.08E+12</td>
<td>5.86E+12</td>
</tr>
</tbody>
</table>
Table 5.6: Particle diameters and corresponding diffusion coefficients.

<table>
<thead>
<tr>
<th>Particle Diameter (µm)</th>
<th>D (m²/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>5.32E-06</td>
</tr>
<tr>
<td>0.003</td>
<td>5.94E-07</td>
</tr>
<tr>
<td>0.008</td>
<td>8.46E-08</td>
</tr>
<tr>
<td>0.01</td>
<td>5.45E-08</td>
</tr>
<tr>
<td>0.02</td>
<td>1.40E-08</td>
</tr>
<tr>
<td>0.03</td>
<td>6.39E-09</td>
</tr>
<tr>
<td>0.08</td>
<td>1.03E-09</td>
</tr>
<tr>
<td>0.09</td>
<td>8.34E-10</td>
</tr>
<tr>
<td>0.1</td>
<td>6.94E-10</td>
</tr>
<tr>
<td>0.2</td>
<td>2.23E-10</td>
</tr>
<tr>
<td>0.3</td>
<td>1.23E-10</td>
</tr>
<tr>
<td>1</td>
<td>2.74E-11</td>
</tr>
</tbody>
</table>

Figure 5.17: Deposition rate to the wall for various particle sizes in healthy and emphysemic models. Inlet concentration of 1E15 particles/m³.
Figure 5.18: Particle deposition vs. time for 0.01 (purple), 0.1 (red), and 1 (green) µm diameter particles in the healthy (solid) and emphysema (dashed) models.

Figure 5.19: Deposition rate per unit area for various particle sizes.

Compare H and E Particle Loading in the Lung

Compare H and E Particle Deposition Rate per Area


6 Chapter 6 Discussion and Conclusion

6.1 Healthy versus Emphysema

On average the global extents, or overall dimensions of the healthy model are half of the emphysema model, which correlates to the healthy alveolar model being approximately 11 times smaller than the emphysema model in size, based upon volume (Table 6.1). Due to the increase size of the emphysematous model, the wall surface area is more than three times greater than the healthy, creating a larger region for particles to deposit. The dimensions are in the range of measured data by Kohlhaufl et al. (1998), which reported an effective airway diameter of 0.86 µm for emphysema. The healthy dimensions are well within the range previously reported by Weibel (1964).

Table 6.1: Geometry comparisons between healthy and emphysema models X, Y, and Z are the overall dimensions of the model if it were to be contained in a box.

<table>
<thead>
<tr>
<th>Model Comparison</th>
<th>Healthy</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>X (mm)</td>
<td>2.11</td>
<td>3.74</td>
</tr>
<tr>
<td>Y (mm)</td>
<td>1.34</td>
<td>3.18</td>
</tr>
<tr>
<td>Z (mm)</td>
<td>1.74</td>
<td>3.49</td>
</tr>
<tr>
<td>Duct Diameter (mm)</td>
<td>0.41</td>
<td>0.63</td>
</tr>
<tr>
<td>Wall Area (mm²)</td>
<td>10.46</td>
<td>33.56</td>
</tr>
<tr>
<td>Volume (mm³)</td>
<td>1.16</td>
<td>12.49</td>
</tr>
</tbody>
</table>

Keeping the models constant, the 1 nm particles are shown to deposit at a rate almost an order of magnitude higher than that 3 nm particles (Table 6.2). Based purely on their diffusion coefficients, this result is well within expectations.

When the particle size is kept constant, and models are compared, the deposition rate of 1 nm particles on the wall of the healthy model, 1.64E+07 particles/s, was almost half that of the emphysema model, 3.12E+07 particles/s, similar results were found in the 3 nm simulations. Based on Equation (3.5) to calculate the wall flux, the concentration gradient is summed over the
entire wall, therefore this result is not surprising since the area for particles to deposit is three
times larger in the emphysema model.

The results reverse when the affect of surface area from the models is taken out of the deposition
rate values. Now, the healthy deposition rate per area (1.57E+06 particles/m²s) becomes greater
than the emphysema deposition rate per area (9.29E+05 particles/m²s) for the 1 nm simulations.
The 3 nm numbers for comparison are shown in Table 6.2, which shows the healthy deposition
per area to be approximately 40% higher than emphysema.

The unsteady state deposition efficiency for the emphysema model is less than for the healthy
model. This trend agrees well with numerical results presented by Sturm and Hoffmann (2004),
who found particle deposition in healthy models to be greater than emphysema models of similar
size. In addition, our results are consistent with decreased deposition in animal models with
emphysema (Damon et al. 1983, Lundgren et al. 1981, Martin et al. 1980, Hahn and Hobbs 1979,
Mauderly et al. 1990).

The steady state deposition efficiencies for the healthy and emphysemic models should approach
100% after infinite time. Based on a simple control volume, if steady state has been reached in
each of the models regardless of particle size, the rate of particles entering must be equal to the
rate of particles depositing in order for mass to be conserved. But the efficiencies shown here
represent our steady state approximation (taken at our steady state criteria) and are therefore less
than 100%. However, the trend does hold; smaller particles will become steady state before
larger particles (96% and 94% for 1 nm and 3 nm, respectively.) and smaller models will reach
steady state sooner than large models (94% for H and 93% for E).

Table 6.2: Healthy vs. Emphysema simulation results for comparison

<table>
<thead>
<tr>
<th></th>
<th>Healthy vs. Emphysema Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 nm</td>
</tr>
<tr>
<td>Healthy</td>
<td>1.64E+07</td>
</tr>
<tr>
<td>Emphysema</td>
<td>3.12E+07</td>
</tr>
<tr>
<td>Healthy</td>
<td>1.57E+06</td>
</tr>
<tr>
<td>Emphysema</td>
<td>9.29E+05</td>
</tr>
<tr>
<td>Steady State Deposition Efficiency (%)</td>
<td>96%</td>
</tr>
</tbody>
</table>
6.2 Comparison to Experimental Data

In order to provide an accurate comparison between the simulations done in this work and experimental alveolar deposition, a residence time used for particle deposition was determined by the pause fraction (4.9%) of a single period. This is likely to produce an underestimate in deposition since this is the very least amount of time that the particles will remain in this region of the lung. Other considerations had to be taken to ensure an accurate comparison was taking place, to do this a local alveolar deposition fraction was calculated. The local alveolar deposition fraction was found by taking the percentage of particles that deposit in the alveolar region, and dividing by the total percentage of particles that entered this region. In order to determine the number of particles entering the alveolar region, the tracheobronchial contribution to particle deposition had to be accounted for and subtracted out. This was all necessary because the only data available from the simulations was particles entering the model and particles depositing, which were used to calculate a deposition fraction. Even after these corrections, our deposition predictions for 1 nm and 3 nm particles are higher than expected based on conventional beliefs.

No experimental studies exist for particle sizes on the scale of this research, therefore, it is required to predict deposition and conclude on expectations based upon the experimental results that are available. Alveolar deposition studies performed by Lippmann and Albert (1969) and Emmett et al. (1982) are difficult to interpret due to the wide range of deposition data, no particular trend is shown to occur that can be applied to particles smaller than 1 µm. However, the results from Kim and Jacques (2000) produce an easy to see trend. As expected, the particle deposition increases with smaller sized particles, likely due to the increased ability to move by molecular diffusion. Similar results were found to occur in this study, as the particle size decreased the deposition fraction increased. If a straight line were to be extended through the experimental data to continue the current trend, it would certainly come close to intersecting the simulation data plotted for the 1 and 3 nm simulations. However, as discussed in the next section, some modeling data suggests that the trend is a decrease in deposition for decreasing size in the nanoparticle range. But again, these conventional beliefs are not yet supported by experimental evidence.
6.3 Comparison to Whole Lung Models in the Literature

Scherer et al. (1972) were some of the first researchers to present the trumpet model in literature. Analytical and numerical models were created to predict pulmonary gas washout, which was later compared to experimental data. Each model solved a form of the convective diffusion equation, but many assumptions were needed to do so, some included 1D axial flow (1D convection and diffusion), infinite cross sectional area at the alveoli, and radial mixing is rapid in comparison to axial mixing. Due to the 1D assumption, no radial diffusion exists and the model does not take into account any wall losses throughout the path from the 1st to 23rd generation. Based on this model, nanosized gas particles would make their way right into the alveoli, and therefore high deposition of nanosized particles in the pulmonary region are possible as we predict in this study. Scherer’s analytical model showed relatively good agreement with experimental for nitrogen gas (0.3 nm sized molecules) washout results presented by Shepard et al. (1957).

The predictions of our study did not agree with the whole lung deposition models, Trumpet and MPPD. The paradox, is that these whole lung particle deposition models are based on the same principals as the model derived from Scherer et al. (1972), but some changes were made. MPPD and Trumpet models solved the convective diffusion equation, using similar assumptions of 1D axial flow but with no axial diffusion. Neither Trumpet nor MPPD model accounted for direct radial diffusion, assuming well mixed, however, unlike Scherer (1972) they did account for losses at the walls. They allowed for the particles to deposit according to the straight tube diffusion deposition efficiency equations (Ingham 1975) in the TB airways and in the alveoli. The alveoli were represented as a tube with the generational average duct diameter and radius. These deposition efficiency equations were derived for a straight tube, with no axial diffusion; resulting in an overestimated deposition of nanosized particles, so axial diffusion was not accounted for in particle transport or deposition. Later, axial diffusion was added to the analytical solution of the convective diffusion equation to enhance particle transport along the airways (Asgharian and Price 2007). They reported that axial diffusion had an impact on pulmonary deposition for particles greater than 10 nm, but smaller particles were found to be completely filtered out by deposition in TB region. This study used the original Ingham (1975) deposition efficiency equations to represent the loss term in the convective diffusion equation,
axial diffusion was not completely accounted for. Therefore deposition of smaller particles in the TB region may be over estimated, reducing transport to the distal. This could be evidenced in their comparisons to experimental results of Kim and Jaques (2000) for particle sizes 1 to 100 nm. For all sizes, deposition predictions in the pulmonary region were smaller than experiment. It is necessary to incorporate axial diffusion in deposition efficiency equations in order to investigate this further.

Using Ingham’s analytical solutions for deposition efficiency in a straight tube, possessing similar dimensions to an alveolar duct and velocity relevant for this region, deposition efficiencies of 100% are found for 1 and 3 nm particles, which agree well with our predictions. It is not clear why these large efficiencies in a single airway do not translate to large efficiencies in the pulmonary region of the MPPD or Trumpet models. However, this discrepancy is consistent with an over-estimation of TB deposition and an underestimation of axial transport.

The trends from the stochastic healthy and emphysemic whole lung models used by Sturm and Hofmann (2004) are very similar to the Trumpet models, in the fact alveolar deposition fractions approach zero for 1 and 3 nm particles. Unfortunately the agreement with Trumpet means a disagreement with the results found in this study. Since they had different TB regions for different diseases, the differences between healthy and emphysema could be in the TB or pulmonary regions. However, Sturm and Hofmann (2004) found their healthy model deposition to be 7% higher than the emphysema or diseased models; this was relative to inhaled particles. In this study, the healthy deposition efficiency was found to be 2-3% higher in the healthy model compared to the emphysema model, which is relative to local particles. The MPPD model is not valid for particles less than 0.01 µm but agrees with Trumpet and Sturm and Hofmann (2004) for larger particles.

In summary, although our model agrees qualitatively well with Scherer (1972), little agreement is shown to occur between the MPPD or Trumpet deposition predictions and the numerical results from this study. MPPD does not claim to be valid for particles less than 10 nm. We expect that the lack of axial diffusion in MPPD and Trumpet is under predicting nanoparticle transport to the alveolar region. Furthermore, the deposition efficiency equation used in the MPPD and Trumpet models neglects axial diffusion, which will over estimate TB deposition, further reducing predictions of alveolar deposition. Our model agrees well with the emphysema
model presented by Sturm and Hofmann (2004), which predicts lower deposition in E compared to H, and to experimental *in vivo* animal data for emphysema.

### 6.4 Limitations

Some limitations exist in this study which are further discussed here along with their effects on the overall results.

#### 6.4.1 Boundary conditions

The inlet boundary condition used in this simulation may not be representative of *in vivo* conditions in the alveolar region of the lung. In order to determine the particle inlet flux (rate of particles entering, particles/s), the deposition of particles throughout the other regions of the lung and mouth must be known precisely. This requires modeling of the TB region and all of the bronchioles distal to the TB region. Additional difficulty is introduced because the rate would change with different particle sizes. This alveolar model can now be combined with previous TB region models to better predict alveolar deposition if this parameter was known.

In this study, the inlet particle concentration (particles/m³) was set to be constant so that the effect of the alveolar region geometry could be isolated for comparative purposes between the two models. Keeping the particle size constant, by setting the inlet concentration equal between the models, the inlet flux of the each model differs.

The inlet duct of the healthy model has a diameter of 0.41 mm, while the emphysema model has an inlet duct of 0.63 mm, resulting in an area increase of 236% to allow particles to enter. If the model volume, or geometry, is kept constant, the dispersion of particles for the same concentration of 1 and 3 nm particles will be vastly different. Based on diffusion coefficient alone, the rate at which 1 nm particles diffuse is over 10 times greater than that of 3 nm particles, which would again change the inlet flux for different particle sizes. Therefore, even though the particle volume concentration (particles/m³) is the same for each model and particle size, the inlet flux (particles/s) into the model is different because the flux is calculated based upon both model geometry (div C) and particle diffusivity (D). We believe that keeping the particle volume concentration constant makes for a better comparison between models than keeping the flux constant between models. This assumes that the airways proximal to the alveoli are
identical for both H and E. Ideally, the concentration at the mouth is held constant between models, and the concentration entering the alveoli would be a function of TB filtering, which could be altered to represent disease.

It is clear this difference in inlet flux between the two models, H and E, would have no factor in the solution for concentration at steady state, as long as the inlet concentration boundary conditions remained the same. Based upon the criteria used for determining steady state (change in % deposition < 0.1%), the steady state times were consistently smaller for cases where the inlet flux was higher. It is unknown whether constant concentration causes a difference in flux that is positive or negative since the flux used for comparison is arbitrary; however, trends show that a higher inlet flux reaches steady state faster. Therefore, smaller particles will reach steady state faster than larger particles.

6.4.2 Convergence Issues

This study was limited to only two particle sizes, 1 nm and 3 nm. Multiple attempts to simulate larger particles were taken, which produced unsatisfactory residual convergence. The lack of convergence caused negative concentrations and fluxes to occur in the solution, which were inaccurate. Due to steady state being reached almost immediately, it was assumed to apply steady state conditions for the entire period of interest, even with particle sizes as small as 1 and 3 nm, the error induced by this assumption was no greater than 4.1%. Using the steady state wall flux for extrapolation, the deposition rate for any particle size can be obtained.

Some important conclusions can be drawn from the extrapolated steady state results. First of all, since the results are taken at steady state, the rate of particles depositing is equal to the rate of particles entering, so the inlet flux is also known. Using the trends discussed in the previous section 6.4.1, for the same model, smaller particles would reach steady state faster because the inlet flux is greater.

6.4.3 Non-Expanding Alveoli

Our previous work has shown diffusion to be the dominant mechanism of particle motion in the alveolar region for particle sizes ranging from 10 nm to as high as 0.1 µm (Harding and Robinson 2010, Berg et al. 2010). Péclet number analyses were performed in two separate alveolar models and found diffusion to dominate convective motion in all regions of the alveolar
sac other than the inlet. Particles used in this work, 1 and 3 nm particles would have even higher tendencies to diffuse based upon their significantly higher diffusion coefficients.

Also shown in the work performed by Harding and Robinson (2010) and Berg et al. (2010), the effects of wall motion on the overall shape of the model is nearly unnoticed. There have been no studies which effectively demonstrate the change in alveolar shape during inhalation. Harding and Robinson (2010) did work combining some of the alveolar shape change articles into a single chart. For a lung volume increase of 80%, the alveolar depth to mouth diameter (D/MD) ratio changed by 0.6. Therefore, since the model walls move very little while expanding and convective motion does not contribute to the motion of the particles, a static wall analysis looking at purely diffusion can be assumed to accurately represent the deposition in the healthy and emphysemic alveolar models for the particle sizes used in this study.

6.4.4 Effects of Sedimentation

If sedimentation were to be incorporated into the current results, it would have very little effect for the 1 nm and 3 nm particles studied in this work. The settling velocities for a 1 nm particle and 3 nm particles are 6.75E-09 and 2.04E-08 m/s, respectively. Therefore, each particle would travel a total of 1.3 and 4 nm during a pause time of 0.2 seconds. The settling velocity only increases to a value of 8.82E-07 m/s for a 0.01 µm particle, but for a 10 µm particle the settling velocity increases to 3.06E-03 m/s. A particle of this size would move a greater distance by gravity and could have an effect on particle deposition totals.

6.5 Conclusions

Two in vivo replica alveolar models, healthy and emphysematous, were created using lung casting and 3D reconstruction techniques refined in our lab. The resulting geometry of the H and E models were consistent with literature; in terms of general features and shapes of the alveoli. The healthy and emphysemic models were simulated to determine deposition of 1 and 3 nm particles by pure diffusion only, for the same localized model inlet particle concentration. Deposition efficiencies showed qualitatively that the healthy model to be greater, which agrees well with in vivo experimental data a stochastic model for emphysema presented in literature. A local alveolar deposition method of measure was used to quantitatively compare simulation results to experimental in vivo measurements and whole lung model results. Poor agreement was
shown for local alveolar deposition fractions in most cases between our results and the experimental measurements and whole lung models. However, our results agreed well with simple straight tube diffusion solutions, which the whole lung models are based upon. It is unknown the cause of the differences, additional work is needed experimentally and numerically to better understand nanoparticle deposition in this region of the lungs.
References


Appendix A – UDF Code

A.1 C code for UDF (FPM_Code.c)

```c
/* ___DEFINITIONS_______________________________________________________*/
/* ______________________________________________________________________*/
#include "fpm_user.h"/* Necessary for FPM to run, udf.h is called in
FPM program */
#include "fpm_bound_flux.h"
/* __________Define and assign constants */
#define MB_MAX_THREADS 50
#define INLET_ID 15  /*Inlet ID from BC panel*/
#define WALL_ID  14  /*Wall ID from BC panel*/
/* __________Define global variables */
FILE *solution, *residual, *fpm_wall_flux, *fpm_inlet_flux,
*fpm_outlet_flux;

real residuals[MAX_EQNS];
int old_iteration, new_iteration;

static void write_mass_balances(Domain *domain);
/* ______________________________________________________________________*/
/* ___FUNCTION HOOKS____________________________________________________*/
/* ______________________________________________________________________*/
/* Hook this to the Define>User-Defined>Function Hooks>Initialization */
/* DEFINE_INIT(udf_name, domain *d) */
/* Creates solution, residual, wall, and inlet files with headings*/
DEFINE_INIT(init_patch, d)
{
    old_iteration=0;

    solution = fopen("solution.plt", "a");
    fprintf(solution, "Run \tTime(s) \tTime Step Size(s) \tTotal 
Iterations \# of Iterations \tUDS-0 Equation \tUDS-1 Equation\n");
    fclose(solution);

    residual = fopen("residual.plt", "a");
    fprintf(residual, "Iteration \tUDS-0 Equation \tUDS-1 
Equation\n");
    fclose(residual);

    fpm_wall_flux = fopen("fpm_wall_flux.plt", "a");
    fprintf(fpm_wall_flux, "Time \tUDS 0 - Wall \tUDS 1 - 
Wall\n");
    fclose(fpm_wall_flux);

    fpm_inlet_flux = fopen("fpm_inlet_flux.plt", "a");
```

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fprint(fpm_inlet_flux, "Time \t\t\t\t\t\tUDS 0 - Inlet\t\t\t\t\t\tUDS 1 - Inlet\n");
fclose(fpm_inlet_flux);

/* Hook this to the Define>User-Defined>Function Hooks>Adjust */
/* DEFINE_ADJUST(udf_name, domain *d) */
/* Extracts residuals and writes them to the file after each iteration */
DEFINE_ADJUST(res_list, domain)
{
    int nw;
    double scaled_res;

    /*Message("\nResiduals for iteration %g",count2[nres-1]);*/
    for(nw=0; nw<MAX_EQNS; ++nw)
    {
        /*Message("\n%i - %s equation:","nw,
            DOMAIN_EQN_LABEL(domain,nw));
        */
        if(strlen(DOMAIN_EQN_LABEL(domain,nw))>0)
        {
            /*Message("\n%\n",scaled_res);*/
            scaled_res=DOMAIN_RES(domain,nw)[nres-1]/DOMAIN_RES_SCALE(domain,nw)[nres-1];
            /*Message("%e
",scaled_res);*/
            residuals[nw] = scaled_res;
        }
    }

    residual = fopen("residual.plt", "a");
    fprintf(residual, "%i \t%e \t%e\n", N_ITER, residuals[65], residuals[66]);
    fclose(residual);
}

/* Hook this to the Define>User-Defined>Function Hooks>Execute At End */
/* DEFINE_EXECUTE_AT_END(udf_name) */
/* Calls flux routine and writes solution information to file */
DEFINE_EXECUTE_AT_END(run_each_dt)
{
    Domain *dom = Get_Domain(1);
    new_iteration = N_ITER - old_iteration;
    write_mass_balances(dom);

    solution = fopen("solution.plt", "a");
    fprintf(solution, "%i \t%e \t%e \t%e \t%e \t%e \n", N_TIME, CURRENT_TIME, CURRENT_TIMESTEP, N_ITER, new_iteration, residuals[65], residuals[66]);
    fclose(solution);
    old_iteration = N_ITER;
}
/* Can be run by selection in Define>User-Defined>Execute On Demand... */
/* DEFINE_ON_DEMAND(udf_name) */
/* Performs same function as EXECUTE_AT_END for cases when time step is 
interrupted and routine is not called */

DEFINE_ON_DEMAND(on_demand)
{
    Domain *dom = Get_Domain(1);

    new_iteration = N_ITER - old_iteration;

    write_mass_balances(dom);

    solution = fopen("solution.plt", "a");
    fprintf(solution, "%i \t%e \t%e \t%e \t%e \t%e \t%e
\t%e\n", N_TIME, CURRENT_TIME, CURRENT_TIMESTEP, N_ITER, new_iteration,
residuals[65], residuals[66]);
    fclose(solution);

    old_iteration = N_ITER;
}

/* Hook this to Solve>Iterate by change time stepping to Adaptive*/
/* DEFINE_DELTAT(udf_name, domain *d) */
/* Controls time stepping parameters */

DEFINE_DELTAT(mydeltat, domain)
{
    real time_step;
    int run = N_TIME;

    if (run <= 10)
        time_step = 1e-5;
    else
    {
        time_step = 1e-4;
    }

    return time_step;
}

/* Routine which extracts flux data from FPM and writes to corresponding
file */

static void write_mass_balances (Domain *domain)
{
    /*static REAL src[MAX_UDS_EQNS], sink[MAX_UDS_EQNS];
    static REAL vsrc[MAX_SPE_EQNS], vsink[MAX_SPE_EQNS];/*/ 
    static REAL _flux[MAX_UDS_EQNS*MB_MAX_THREADS]/*,
    _vflux[MAX_SPE_EQNS*MB_MAX_THREADS]*/;
    REAL *flux, *vflux*/;

    Thread *t, *t0;
int i_thread[MB_MAX_THREADS];
int i;
int i_mb, n_mb;

i_mb = 0;
flux = _flux - MAX_UDS_EQNS;
/*vflux = _vflux - MAX_SPE_EQNS;/*

thread_loop_f (t, domain)
{
    if (i_mb >= MB_MAX_THREADS)
    {
        Message("Max number of threads exceeded\n");
        break;
    }

    t0 = THREAD_T0 (t);

    if (!BOUNDARY_FACE_THREAD_P(t) || !THREAD_STORAGE (t,
        SV_UDS_I(first_uds)) ||
        THREAD_TYPE (t) == THREAD_F_AXIS || THREAD_TYPE (t)
        == THREAD_F_SYMMETRIC || !FLUID_THREAD_P(t0))
        continue;

    i_thread[i_mb] = THREAD_ID(t);
    flux += MAX_UDS_EQNS;
    /*vflux += MAX_SPE_EQNS;*/
    i_mb++;
}

n_mb = i_mb;

for (i_mb = 0, flux = _flux/*, vflux = _vflux*/; i_mb <
    n_mb; i_mb++, flux += MAX_UDS_EQNS/*, vflux += MAX_SPE_EQNS*/)
{
    /*FPM_Message ("%10d", i_thread[i_mb]);*/

    if (i_thread[i_mb]==WALL_ID)
    {
        fpm_wall_flux = fopen("fpm_wall_flux.plt","a");
        fprintf(fpm_wall_flux,"%e", CURRENT_TIME);

        for (i = first_uds; i < last_uds; ++i)
        {
            fprintf(fpm_wall_flux,"\t\t%e",RIT_uds_flux[i_mb][i]);
        }
        fprintf(fpm_wall_flux,"\n");
        fclose(fpm_wall_flux);
    }

    if (i_thread[i_mb]==INLET_ID)
    {
        fpm_inlet_flux =
            fopen("fpm_inlet_flux.plt","a");
        fprintf(fpm_inlet_flux,"%e", CURRENT_TIME);
for (i = first_uds; i < last_uds; ++i)
{
    fprintf(fpm_inlet_flux, "\t\t%e", RIT_uds_flux[i_mb][i]);
    fprintf(fpm_inlet_flux, "\n");
    fclose(fpm_inlet_flux);
}

/*for (i = 0; i < GAS_MAXSPECIES; i++)
{
    FPM_Message ("|%14.6e", vflux[i]);
    vbal[i] += vflux[i];
    species_flux[i] = vflux[i];  //STORING SPECIES FLUXES SO THEY
    ARE AVAILABLE OUTSIDE OF do_mass_balances
}
FPM_Message ("\n");*/

FPM_Message ("\n");

/*FPM_Message ("%10s", "Source:  ");
for (i = first_uds; i < last_uds; ++i)
{
    FPM_Message ("|%14.6e", src[i]);
}
for (i = 0; i < GAS_MAXSPECIES; i++)
{
    if (gas_udm_map[i] < 0) continue;
    FPM_Message ("|%14.6e", vsrc[i]);
}
FPM_Message ("\n");
FPM_Message ("%10s", "Sink:    ");
for (i = first_uds; i < last_uds; ++i)
{
    FPM_Message ("|%14.6e", sink[i]);
}
for (i = 0; i < GAS_MAXSPECIES; i++)
{
    if (gas_udm_map[i] < 0) continue;
    FPM_Message ("|%14.6e", vsink[i]);
}
FPM_Message ("\n");
FPM_Message ("%10s", "Balance:  ");
for (i = first_uds; i < last_uds; ++i)
A.2 C code for header (fpm_bound_flux.h)

/* Extracts necessary data and variables from inside FPM program and allows for use in UDF code */
#define MB_MAX_THREADS2 50  /* Taken from definition just before do_mass_balances */
extern REAL RIT_uds_flux[MAX_UDS_EQNS*MB_MAX_THREADS2][MAX_UDS_EQNS],
RIT_species_flux[MAX_SPE_EQNS*MB_MAX_THREADS2][MAX_SPE_EQNS];